Rapamune®(sirolimus) Oral Solution

Summary for Presentation to
The Subcommittee of the Antiviral Drugs Advisory Committee on Immunosuppressive Drugs

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1 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AZA	Azathioprine
Ca^{2+}	Calcium
CK	Creatine kinase
CsA	Cyclosporine (cyclosporin A)
ESP	Electrospray
FK506	Tacrolimus (Prograf®)
FKBP	FK binding protein
GFR	Glomerular filtration rate
HPLC	High-performance liquid chromatography
IL	Interleukin
ISS	Integrated Summary of Safety
LC	Liquid chromatography
LDH	Lactate dehydrogenase
MS	Mass spectrometry
mTOR	Mammalian target of rapamycin
NDA	New Drug Application
PCP	*Pneumocystis carinii* pneumonia
PTDM	Posttransplant diabetes mellitus
PTLD	Posttransplant lymphoproliferative disease
RAPA	Rapamune (sirolimus, rapamycin)
TEAE	Treatment-emergent adverse event
WBC	White blood cell

2 EXECUTIVE SUMMARY

The information presented here summarizes data submitted in the original new drug application (NDA) as well as data submitted in subsequent correspondence with the FDA.

2.1 Indication and Dose Recommendation

Rapamune (sirolimus, rapamycin) is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used in a regimen with cyclosporine (CsA) and corticosteroids.

For most patients, the recommended maintenance dose is Rapamune 2 mg/day. For patients with a high risk of rejection, the recommended maintenance dose is Rapamune 5 mg/day.

2.2 Mechanism of Action

Rapamune, a macrocyclic lactone isolated from *Streptomyces hygroscopicus*, is a powerful immunosuppressive agent that modulates the immune response by inhibiting the activity of a regulatory protein critical for coordination of the cellular events required for cells to move from the G_1 to the S phase of the cell cycle.[1,2]

Rapamune inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. In cells, Rapamune binds to the immunophilin FK binding protein (FKBP-12) to generate an immunosuppressive complex. Unlike CsA and tacrolimus, the Rapamune:FKBP complex has no effect on calcineurin activity. Rather, this complex binds to and inhibits the activation of a specific cell cycle regulatory protein called the mammalian target of rapamycin (mTOR). mTOR is a key regulatory kinase and its inhibition by Rapamune suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

In in vitro studies, Rapamune inhibits proliferation of T lymphocytes, B lymphocytes, and vascular and bronchial smooth muscle cells induced by cytokines and growth factors. Because Rapamune affects lymphocyte activation by a different mechanism, activation stimuli that resist inhibition by CsA and tacrolimus (FK506) have been shown to

be sensitive to Rapamune. Rapamune also affects B cell activation and antibody production. These effects contribute to the immunosuppressive properties of Rapamune.

2.3 Key Results from Supportive Phase II Clinical Data

2.3.1 Study 0468E1-203-CA, EU, US and GL

Study 203 was conducted to compare 1.0, 3.0, or 5.0 mg/m^2/day Rapamune, administered by body surface area, with placebo administered with corticosteroids and full or reduced doses of CsA (as defined by whole blood trough concentration). Key efficacy results are shown below:

- Prophylactic treatment of primary, mismatched renal allograft recipients with full dose CsA/corticosteroid therapy plus Rapamune significantly reduced the incidence of the first biopsy-confirmed acute rejection episode.

- Prophylactic treatment of primary, mismatched renal allograft recipients with reduced-dose CsA/corticosteroid therapy plus Rapamune also reduced the incidence of the first biopsy-confirmed acute rejection episode.

Rapamune was well tolerated in study 203. The adverse event profile was similar to what was subsequently seen in controlled phase III studies, with the exception of pneumonia, which occurred more frequently in the 3 mg/m^2/day Rapamune plus full-dose CsA group. Some of these cases of pneumonia were associated with *Pneumocystis carinii*, including a single-center outbreak in which routine prophylaxis had not been employed. Prophylaxis against *P. carinii* pneumonia (PCP) was required in the phase III protocols. Three (3, 2.4%) malignancies were reported in the Rapamune groups (2 skin carcinomas and 1 lymphoma) at 1 year. There were 13 deaths (10.4%) in the Rapamune groups, mainly due to infection or cardiovascular events. Graft function, measured directly by isotopic glomerular filtration rate (GFR) and calculated indirectly by the Nankivell formula, did not differ significantly between treatment groups during the first year following transplantation.

2.3.2 Studies 0468E1-207-EU and -210-EU

Studies 207 and 210 were designed to compare Rapamune with CsA as primary (base) therapy in patients with renal allografts. These were concentration-controlled trials in which daily doses of Rapamune were adjusted to achieve steady-state whole blood trough levels. The results of these studies demonstrated that treatment with Rapamune as base

immunosuppressive therapy (without CsA) results in better graft function over time than CsA-based therapy, but the incidence of biopsy-confirmed acute rejection may not be different.

Results confirmed that the safety profile of Rapamune was distinct from that of CsA. The incidence of diarrhea, arthralgia, epistaxis, hyperlipidemia, leukopenia, pain, thrombocytopenia, and certain infections was higher with Rapamune. There were favorable trends for renal function with Rapamune. Certain other laboratory values were also affected by Rapamune. The incidence of hypertension, gum hyperplasia, hyperuricemia, tremor, and asthenia was higher with CsA. There were no differences between the treatment groups in patient and graft survival.

2.4 Key Results of Phase III Clinical Trials

The safety and efficacy of Rapamune for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter controlled trials. These studies compared two dose levels of Rapamune oral solution (2 mg and 5 mg, once daily) with azathioprine (study 0468E1-301-US, referred to as study 301) or placebo (study 0468E1-302-GL, referred to as study 302) when administered in combination with CsA and corticosteroids. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. The results showed that at doses of 2 mg/day and 5 mg/day, Rapamune reduced the incidence of the primary endpoint and the incidence of biopsy-proven acute rejection at 6 months following transplantation to a significantly greater extent than either azathioprine and placebo. Patient and graft survival at 1 year were excellent in all groups. The graft and patient survival rates at 1 year were equivalent in the Rapamune- and control-treated patients.

In these studies, adverse reactions that were significantly more frequent in the Rapamune groups than in either control group included peripheral edema, diarrhea, arthralgia, lymphocele, and *Herpes simplex*. Dose-related elevations of triglyceride and cholesterol levels and decreases in platelet counts and hemoglobin values have occurred in some patients receiving Rapamune.

3 INTRODUCTION

Acute allograft rejection within the first 6 months following transplantation continues to be a significant clinical problem despite recent advances in immunosuppressive regimens.[3,4,5,6,7,8] Early acute rejection episodes (those diagnosed within the first 6 months after transplantation), especially those of severe grade or with permanent functional deterioration, are frequently associated with a higher incidence and an earlier onset of chronic rejection and shortened graft longevity.[9,10,11,12,13] Acute rejection episodes also require additional immunosuppression with corticosteroids and/or antibody preparations, thus increasing the risk of infectious complications and malignancies and prolonging hospital stays.[4,14,15] Thus, an immunosuppressive regimen that included a safe drug with a novel mechanism of action and that improved acute allograft rejection rates while maintaining or improving graft and patient survival would represent an advancement in organ transplantation.

Rapamune, a macrocyclic lactone isolated from *Streptomyces hygroscopicus*, is a powerful immunosuppressive agent that modulates the immune response by inhibiting the activity of a regulatory protein critical for coordination of the cellular events required for cells to move from the G_1 to the S phase of the cell cycle.[1,2] The mechanism of Rapamune is unique in that this regulatory protein is not targeted by CsA or other agents currently used in transplantation. Whereas CsA and tacrolimus (FK506) achieve their effects by inhibiting calcineurin and reducing IL-2 expression,[16,17,18,19] Rapamune inhibits IL-2-mediated signal transduction but has no effect on calcineurin activity.[1,2,20]

The macrocyclic immunosuppressive agents, including Rapamune, CsA, and tacrolimus, bind to specific cytosolic proteins called immunophilins to achieve their immunosuppressive activity.[21,22] The complexes of CsA or tacrolimus with their respective immunophilins (cyclophilin and FKBP-12, respectively) inhibit calcineurin, a Ca^{2+}/calmodulin-dependent serine/threonine phosphatase required for the production of IL-2 and early activation of T lymphocytes, ie, the transition from the G_0 to the G_1 phase of the cell cycle.[16,17,18,19] Rapamune also binds FKBP12, but unlike the tacrolimus:FKBP12 complex, the Rapamune:FKBP complex has no effect on calcineurin activity.[16,23,24] Rather, this complex binds to a specific cell cycle regulatory protein called mTOR and inhibits its activation.[25,26,27,28,29] The inhibition of mTOR results in suppression of cytokine-driven (IL-2,

IL-4, and IL-15) T-lymphocyte proliferation, inhibiting the progression from G_1 to the S phase of the cell cycle.[20]

Rapamune is synergistic with CsA both in vitro and in vivo[30,31,32,33] and has a side effect profile that largely differs from that of other immunosuppressive agents.[34,35,36,37] The differential effects of Rapamune and CsA provide the rationale for combining them in an immunosuppressive regimen.

Previous clinical studies have demonstrated that Rapamune in combination with CsA (Sandimmune)-based regimens is more effective than other agents in reducing the incidence of acute rejection in recipients of primary, mismatched renal allografts, without the expense of increased toxicity.[2]

Two adequate and well-controlled phase III studies were performed to compare two standard immunosuppressive regimens (double and triple therapy) to a Rapamune plus CsA/corticosteroid regimen in recipients of primary, mismatched renal allografts. Both studies defined the safety profile of Rapamune and demonstrated that the efficacy of the Rapamune plus CsA/corticosteroid regimen was greater than that of standard immunosuppressive regimens. These studies compared two dose levels of Rapamune oral solution (2 mg and 5 mg, once daily) with azathioprine (study 301) or placebo (protocol 302) when administered in combination with CsA and corticosteroids.

4 TABLE OF STUDIES

The NDA for Rapamune oral solution was submitted on 15 December 1998. The table of studies is provided in Section 11. It gives the protocol and report numbers, a brief description of the design of each clinical study, and the number of patients/subjects enrolled.

The studies are grouped by study type and patient population:

- Adequate and well-controlled trials in renal allograft recipients
- Long-term studies in renal allograft recipients
- Concentration-controlled, base therapy studies in renal allograft recipients
- Safety, tolerance, and pharmacokinetic studies in renal allograft recipients; phase II studies in renal and cardiac allograft recipients
- Safety, tolerance, and pharmacokinetic studies in healthy subjects
- Special populations
- Non-IND studies
- Discontinued formulations

5 CLINICAL PHARMACOKINETICS

5.1 Overview

Rapamune pharmacokinetic profiles and/or trough concentration profiles were studied in a total of 690 healthy subjects and patients from 44 clinical studies. Complete concentration-time profiling was conducted in 40 studies to estimate Rapamune pharmacokinetic parameters.

The following populations were studied: healthy subjects, patients with stable renal allografts, post-renal transplant patients, patients with renal allografts with renal compromise, those with renal allografts with high risk of rejection, patients with liver allografts, patients with psoriasis, and patients with hepatic impairment. In addition, pediatric patients who had stable chronic renal failure and were receiving hemodialysis or peritoneal dialysis were also studied.

5.2 Pharmacokinetics Summary: Absorption, Distribution, Metabolism, Excretion (ADME), Special Populations, and Drug Interactions

- *Absorption*: Rapamune is rapidly absorbed after oral administration, with mean time to peak concentration of 0.90 hours in healthy subjects after single oral doses and 2.0 hours in renal transplant recipients after multiple oral doses. The mean systemic availability of sirolimus was 14%. Upon repeated administration, the average whole blood sirolimus concentration over a dose interval (C_{ave}) was increased 2.6 fold.

- *Distribution*: The mean blood-to-plasma ratio of Rapamune was 36 in stable renal allograft recipients, indicating that Rapamune is extensively partitioned into formed blood elements. The mean oral-dose volume of distribution (V_{ss}/F) of Rapamune was 11.6 L/kg. Rapamune is extensively bound (approximately 92%) to human plasma proteins. In human subjects, the binding of Rapamune was shown mainly to be associated with serum albumin (97%), α_1-acid glycoprotein, and lipoproteins.

- *Metabolism*: Rapamune is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Rapamune is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including

hydroxy, demethyl, didemethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. The glucuronide and sulfate conjugates are not present in any of the biologic matrices. The demethyl and hydroxy metabolites each show ≤ 30% of the in vitro immunosuppressive activity of Rapamune.

- *Elimination*: After a single dose of [^{14}C]Rapamune in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine.

- *Special populations*:

  * *Gender and race*: No adjustment of dose regimen is recommended for men and women. There were no statistically significant effects on pharmacokinetic parameters due to ethnic origin. However, intersubject variabilities (%CV) in the weight-normalized oral-dose clearance (CL/F/WT) were large among all ethnic groups. Thus, white (n = 382), black (n = 94), Asian (n = 7), Hispanic (n = 66), and other (n = 21) subjects, showed intersubject %CVs in CL/F/WT of 61%, 43%, 44%, 61%, and 44%, respectively.

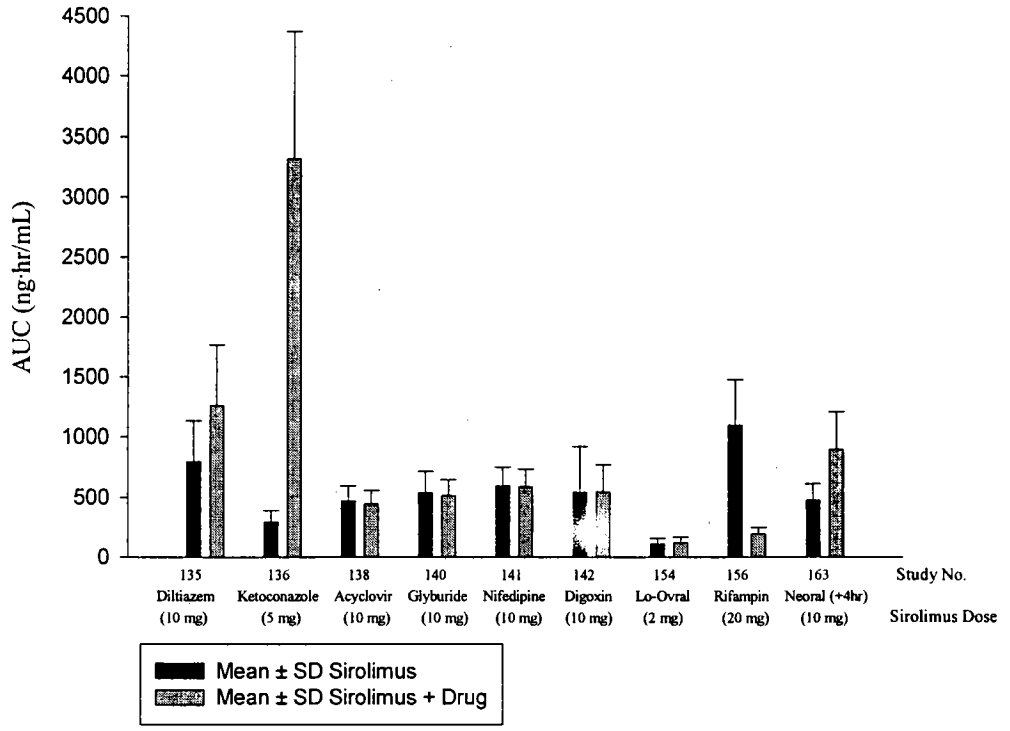
  * *Age*: Oral dose clearance decreases with age, although this reduction in clearance is not clinically important. Pediatric patients may need a 1.5- to 2-fold increase in the maintenance dose (mg/m^2) to achieve concentrations similar to those in adult patients. However, due to the present uncertainty of Rapamune pharmacokinetics in pediatric transplant patients receiving concomitant oral doses of both Rapamune and CsA, whole blood Rapamune concentrations should be monitored to detect any abnormally low concentrations.

  * *Hepatically impaired patients.* It is recommended that the dose of Rapamune be reduced by one-third in patients with chronic hepatic impairment who undergo renal transplantation and/or in patients who develop overt hepatic dysfunction subsequent to transplantation.

- *Food-Drug Interaction*: After a high fat-meal, the rate and extent of Rapamune absorption are changed. The maximum expected mean increase in AUC after a high-fat meal is 35%, due to increased bioavailability rather than decreased elimination. Rapamune may be given with or without food because the variability in absorption caused by food would not be expected to affect safety or efficacy. Orange juice and water may be used interchangeably as administration liquids, but Tang increased AUC by 20% compared with water.

- *Drug-Drug Interactions*: Figure 5.2A presents the comparative mean (± SD) sirolimus exposures (AUC) in healthy subjects when sirolimus is given alone and in combination with 9 potentially interacting drugs.

FIGURE 5.2A. COMPARATIVE RAPAMUNE (SIROLIMUS) EXPOSURE AMONG PHASE I DRUG-INTERACTION STUDIES



There were no clinically significant interactions on sirolimus pharmacokinetics after concomitant administration of Rapamune with the agents acyclovir, glyburide , digoxin, nifedipine, and Lo-Ovral. However, clinically significant interactions were observed after the concomitant administration of Rapamune with diltiazem, ketoconazole, rifampin, and cyclosporine (Neoral). The most dramatic effects on sirolimus pharmacokinetics were observed after co-administration with ketoconazole and rifampin. Ketoconazole increased sirolimus exposure by 990%, while rifampin decreased sirolimus exposure by 82%. Cyclosporine (Neoral) increased the exposure of sirolimus by 80% when Rapamune was administered 4 hours after Neoral (staggered) and by 230% when the 2 drugs were administered simultaneously. The staggered regimen used in healthy subjects simulated the Rapamune/Neoral regimen used in pivotal phase III sirolimus clinical trials. By contrast,

Rapamune did not effect the pharmacokinetics of any of the above agents in studies with healthy subjects.

Pharmacokinetic studies in patients permitted investigation of drug interactions with prednisolone, trimethoprim/sulfamethoxazole, and cyclosporine (either as Sandimmune or Neoral). A 2-week course of sirolimus therapy in stable renal transplant patients did not produce a clinically significant effect on prednisolone/prednisone/cortisol pharmacokinetics. A single dose of trimethoprim/sulfamethoxazole in de novo renal transplant patients receiving sirolimus/azathioprine/steroid therapy did not affect the pharmacokinetics of sirolimus. A comparison between cohorts of psoriasis patients receiving Rapamune alone and simultaneously with Sandimmune showed that simultaneous administration of the 2 agents consistently increased whole blood sirolimus trough concentrations by 75%.

Although single-dose Rapamune had no effect on the pharmacokinetics of single-dose Neoral (CsA microemulsion) in healthy subjects, staggered multiple oral doses of Rapamune and Neoral in the 301 and 302 phase III de novo renal transplant patients affected both CsA pharmacokinetics and the doses of Neoral needed to achieve target CsA concentrations. CsA oral-dose clearances declined for the 2 mg and 5 mg Rapamune dose groups as shown by mean estimates for CsA CL/F/WT of 566 (placebo), 397 (2 mg), and 340 (5 mg) mL/h/kg, respectively. CsA dose reductions of approximately 10% and 15% were required in the 2 mg and 5 mg Rapamune dose groups to achieve target CsA concentrations.

Diltiazem increased the bioavailability of Rapamune, and dose adjustments should be considered; Rapamune did not affect the pharmacokinetics of diltiazem. Multiple doses of ketoconazole significantly increased the extent of absorption and Rapamune exposure, which may result in high levels of Rapamune. When administered with ketoconazole, whole blood Rapamune concentrations should be monitored and doses adjustments should be considered. When rifampin is given with Rapamune, exposure to Rapamune is significantly decreased; a 5-fold increase in the oral dose of Rapamune should be initiated to stimulate mean pre-rifampin whole blood levels, and Rapamune trough levels should be monitored.

6 DESIGN OF CLINICAL STUDIES

6.1 Phase III Study Design

Two pivotal, double-blind, comparative, large-scale, multicenter phase III trials of Rapamune were conducted in recipients of a first renal transplant. Study 301 was conducted in the United States and study 302 was conducted in Australia, Canada, Europe, and the United States. The major design characteristics of these studies are summarized in Table 6.1A.

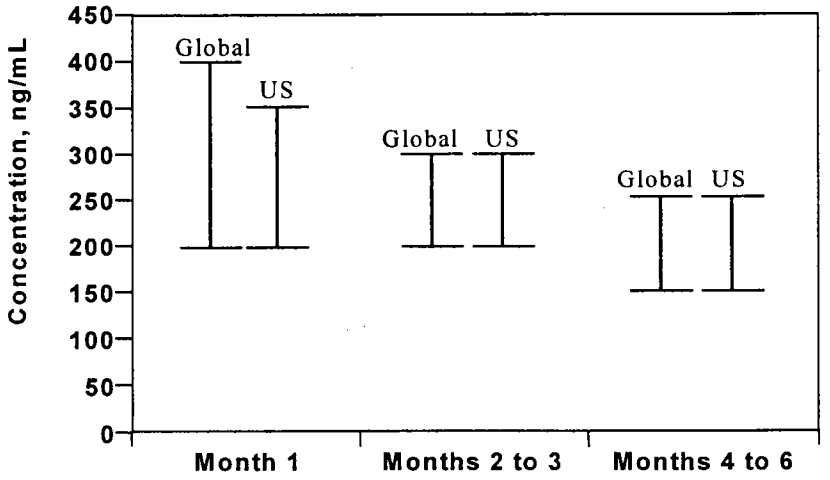
TABLE 6.1A. DESIGN CHARACTERISTICS OF STUDIES 301 AND 302

	Study (0468E1-)	
Study Design Characteristic	301	302
Background immunosuppression	Cyclosporine and Corticosteroids	Cyclosporine and Corticosteroids
Randomization ratio • Groups to which patients were randomly assigned	2:2:1 • Rapamune 2 mg/day:[a] • Rapamune 5 mg/day:[b] • Azathioprine 2 to 3 mg/kg[c]	2:2:1 • Rapamune 2 mg/day:[a] • Rapamune 5 mg/day:[b] • Placebo
Time of randomization	After transplant	Before transplant
Stratification	Center/race	Center/donor origin
Antibody induction	Prohibited	Prohibited
Prophylaxis	Cytomegalovirus and *Pneumocystis carinii* pneumonia	Cytomegalovirus and *Pneumocystis carinii* pneumonia
Number of study centers	38	34
Number of patients	719	576
Inclusion criteria	• First transplant - Cadaveric donor - Living donor (related or unrelated) • Age 13 years or greater • Written informed consent	• First transplant - Cadaveric donor - Living donor (related or unrelated) • Age 13 years or greater • Written informed consent
Exclusion criterion	HLA-identical living related donor	HLA-identical living related donor

a: Loading dose (0 to 48 hours after transplant) for 2 mg/day Rapamune was 6 mg/day.
b: Loading dose (0 to 48 hours after transplant) for 5 mg/day Rapamune was 15 mg/day.
c: Loading dose (0 to 48 hours after transplant) for azathioprine was 5 mg/kg.

The target trough CsA concentrations for studies 301 and 302 are shown in Figure 6.1A.

FIGURE 6.1A. TARGET TROUGH CYCLOSPORINE CONCENTRATION, STUDIES 301-US AND 302-GL



Patients in studies 301 and 302 received high doses on days 1 through 4, with gradual tapering to 10 mg/day by month 6 and to between 5 and 10 mg/day by month 12.

The patients were followed for at least one year. Discontinued patients were evaluated for acute rejection, graft loss, and serious adverse events including infection and malignancy.

6.2 Phase III Study Design Issues

General issues, such as the rationale for choice of comparators, Rapamune dose selection, the Rapamune dose administration interval, rationale for stratification, and choice of the primary efficacy endpoint will be discussed in this section.

6.2.1 Comparative Immunosuppressive Regimens

All patients received base immunosuppression of CsA and corticosteroids as described (section 6.1). Both comparative regimens (azathioprine or placebo plus CsA and corticosteroids) are considered to be standard treatment for recipients of first kidney grafts at most participating study centers, because they have been shown to provide acceptable results in terms of patient and graft survival. Both comparator treatments had the benefit of being used widely as standard therapy in the transplant centers.

Other immunosuppressive drugs were considered. Tacrolimus has a mechanism of action similar to that of CsA, but positive phase II results had been obtained with the Rapamune/CsA combination and tacrolimus was not approved for treatment of renal allograft recipients. Most centers had little experience with MMF, since it either had been just recently approved or had not yet been approved for use at the start of these studies and would have been difficult to blind. Antibody induction therapy was prohibited because its long-term benefit had not been demonstrated and because in phase II studies of Rapamune a significant reduction in the incidence of the first biopsy-confirmed acute rejection had been obtained in the absence of antibody induction therapy.

6.2.2 Rationale for Phase III Dose Selection

Doses for phase III were chosen based upon the phase II dose-ranging trial experience (study 203). This trial explored the effect of Rapamune doses given by body surface area, administered with prednisone and ordinary or low doses of CsA (as defined by whole-blood trough concentration). The addition of Rapamune at varying doses provided incremental protection from acute rejection. Intersubject normalized oral dose clearance varied 7 fold, far greater than the 1.8 fold variation in body surface area noted in this study. Simulations of trough ranges using fixed doses of 2 and 6 mg closely reflected the actual trough concentrations measured in phase II at 1 mg/m^2 and 3 mg/m^2 respectively; adjustment of dose by body surface area appeared unnecessary. The other finding relevant to dose was the lack of a trough concentration effect relationship, a finding that mitigated against trough concentration control of Rapamune when administered with CsA and prednisone. These findings led to the testing of 2 fixed daily doses in blinded phase III trials.

In the phase III studies, Rapamune was administered as a fixed daily dose. Dose administration was initiated as soon as the patient could tolerate oral or nasogastric medication (within 24 to 48 hours after transplantation). A loading dose (three times the

maintenance dose) was administered. The need for a loading dose to establish adequate blood levels of Rapamune was demonstrated in phase I and II studies (studies 112 and 203). Study medication was administered 4 hours after the morning dose of CsA (Neoral) because exposure to Rapamune is increased when Rapamune is coadministered with CsA (Neoral); this effect is attenuated when administration of the two drugs is separated by at least 4 hours. Concurrent administration of CsA and Rapamune results in an increase of approximately 45% in whole blood sirolimus exposure (AUC) without affecting CsA exposure. Once-daily administration of Rapamune has been shown to maintain therapeutic levels of Rapamune (studies 112 and 123).

6.2.3 Stratification

Each study was stratified by two variables. Both studies were stratified by center. Because study 301 was conducted exclusively in the United States, it was expected that this study would enroll a greater proportion of black patients than study 302. Therefore, stratification by ethnic origin (black or non-black) within center was chosen for study 301. The other variable of great interest was donor origin (cadaver vs living); therefore, stratification by donor origin within center was chosen for study 302.

6.2.4 Choice of Primary Efficacy Endpoint

The primary composite endpoint for both studies was efficacy failure, defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death within the first 6 months after transplantation. This composite endpoint represented the best means to assure that the three most important events in the posttransplantation period were appropriately captured and analyzed. Each component of the composite endpoint was easily measurable, clinically relevant, and therefore considered to be an important and well-accepted measure of the effectiveness of an immunosuppressive drug in transplant recipients.

Acute rejection and graft loss are defined in Table 6.2.4A.

TABLE 6.2.4A. DEFINITIONS OF COMPONENTS OF THE PRIMARY COMPOSITE ENDPOINT

Endpoint	Definition
Acute Rejection	• Interpreted by site pathologist[a] • Banff 1993 Grade I or higher
Graft Loss	• Functional: Dialysis for 56 or more consecutive days, even if function recovered • Physical: Nephrectomy

a: A correlation between the local readings and readings from a central pathologist was made and the Kappa statistic of agreement showed satisfactory agreement between the local and central pathologist in each study.

7 EFFICACY

7.1 Overview of Results of Phase III and Supportive Studies

One thousand two hundred ninety-five (1295) patients were enrolled in the 2 phase III studies: 719 patients in the azathioprine-controlled study (301) and 576 patients in the placebo-controlled study (302). These 2 studies were similar but not identical in design and results from the intent-to-treat primary and secondary efficacy analyses were comparable in both studies. During the first 6 months after transplantation, Rapamune groups demonstrated the following results when compared to a control group (azathioprine or placebo) for the prophylaxis of acute rejection in cadaveric or living (mismatched), primary renal allograft recipients who received concomitant CsA/corticosteroid therapy:

Efficacy Failure:

- Significant reduction of the rate of efficacy failure (the occurrence of biopsy-confirmed acute rejection, graft loss or death).

Acute Rejection:

- Significant reduction of the incidence of first biopsy-confirmed acute rejection episodes.
- Significant reduction in the incidence of any first acute rejection episode.
- Significant reduction in the use of anti-T lymphocyte antibody therapies to treat the first biopsy-confirmed acute rejection episode.
- Alteration of the distribution of histologic severity grade of acute rejection toward more mild rejections.

Other Endpoints:

- Significant reduction in the incidence of treatment failure.
- Excellent 1 year patient and graft survival rates (≥ 95% and ≥ 89.9%, respectively).

A total of 345 patients were enrolled in supportive phase II studies (203, 207, and 210). The primary efficacy endpoint for these studies was the incidence of the first biopsy-confirmed acute rejection episode. Secondary endpoints were patient and graft survival and graft function over time. These supportive studies demonstrated the following results when

compared to a control group for the prophylaxis of acute rejection in primary renal allograft recipients:

Acute Rejection

- Prophylactic treatment of primary, mismatched renal allograft recipients with full dose CsA/corticosteroid therapy plus Rapamune significantly reduced the incidence of the first biopsy-confirmed acute rejection episode (study 203).
- Prophylactic treatment of primary, mismatched renal allograft recipients with reduced dose CsA/corticosteroid therapy plus Rapamune also reduced the incidence of the first biopsy-confirmed acute rejection episode (study 203).

Graft Function

- Treatment with Rapamune as base immunosuppressive therapy (without CsA) results in better graft function over time than CsA-based therapy but the incidence of biopsy-confirmed acute rejection may not be different (studies 207 and 210).

7.2 Primary Efficacy Endpoint

The primary efficacy endpoint in both phase 3 trials (studies 301 and 302) was the rate of efficacy failure within the first 6 months after transplantation. The 6 month efficacy window was defined from 154 to 194 days after transplantation. Efficacy failure was defined as the first occurrence of 1) biopsy-confirmed acute rejection, 2) graft loss (functional [> 56 days of continuous dialysis] or physical), or 3) death. Patients defined as lost to follow-up were scored as efficacy failures, regardless of treatment assignment for the primary analysis.

The prospectively-defined primary endpoint included first biopsy-confirmed acute rejection episodes treated within 48 hours from the time of renal biopsy. However, this pre-defined treatment window resulted in the exclusion of a substantial number of first biopsy-confirmed rejections. In collaboration with FDA, the analysis of the primary efficacy endpoint includes all first biopsy-confirmed acute rejections. Further, all analyses of endpoints incorporating acute rejection are based upon this definition of biopsy-confirmed acute rejection.

7.3 Secondary Endpoints

- Patient and graft survival were analyzed 1 year after transplantation.
- Additional secondary (6-month) endpoints included:
    1) incidence of the first acute rejection (biopsy confirmed and all first acute rejection episodes).
    2) histological grade of first acute rejection episode.
    3) use of antibody therapy to treat the first acute rejection episode analyzed.
    4) incidence of treatment failure (defined as occurrence of acute rejection or premature withdrawal from study drug for any reason during the first 6 months after transplantation).

7.4 Determination of Sample Size

For the purposes of determining sample size, efficacy failure rates at 6 months were estimated to be 18% for Rapamune-treated patients, 36% for the azathioprine control group, and 40% for the placebo control group. The randomization ratio was 2:2:1.1, Rapamune 2 mg/day to Rapamune 5 mg/day and control groups, respectively.

For study 301, 234 patients were needed in each of the two Rapamune treatment groups and 132 patients in the azathioprine control group, in order to have 90% power to declare a significant difference in each comparison under the conditions described; a minimum total of 600 patients was required. For study 302, 164 patients were needed in each of the two Rapamune treatment groups and 92 were needed in the placebo control group in order to have 90% power to declare a significant difference in each comparison under the conditions described; a minimum total of 420 patients was required. Each study enrolled patients beyond the minimum number stated in the protocol in order to ensure that the data from approximately 500 patients at, or above, the recommended Rapamune dose level would be available for safety analysis.

7.5 Demographic and Other Baseline Characteristics

The demographic and baseline characteristics for all patients assigned to treatment in the studies are summarized in Table 7.5A. Table 7.5B summarizes donor source information and primary etiology of end-stage renal disease. There were no statistically significant differences with respect to these baseline parameters across treatment groups

within each study with the exception of sex in study 301. In this study, a significantly ($p < 0.001$) higher proportion of females subjects were assigned to the azathioprine group (43%) than to the Rapamune groups (27%, Rapamune 2 mg/day; 38%, Rapamune 5 mg/day).

There were observable differences in the patient distribution with respect to ethnic origin and the donor graft type between the two studies; a higher proportion of black patients were enrolled in study 301 than in study 302 (23% and 11%, respectively), and a lower proportion of patients received cadaveric grafts in study 301 than in study 302 (66% and 77%, respectively). Study 301 was prospectively stratified by race and study 302 by donor origin.

Pooled demographic and baseline characteristics for the two studies, derived from the two tables below, showed that the proportion of women enrolled in the studies was approximately one third (34%) of the total patient population. The majority (82%) of the patient population was of ethnic origin other than black (18%). The average age of the patient population was 45.6 years. The etiologies of end-stage renal disease leading to transplantation were diverse; glomerulonephritis and hypertension were the most common. When the characteristics were compared between combined treatment groups, the azathioprine group had a greater proportion of women, a greater proportion of black patients, and a smaller proportion of patients who received transplants because of glomerulonephritis than the other treatment groups.

TABLE 7.5A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF PATIENTS ENROLLED IN STUDIES 301 AND 302

Characteristic	Rapamune 2 mg/day Study 301 [a]	Rapamune 2 mg/day Study 302 [b]	Rapamune 5 mg/day Study 301 [a]	Rapamune 5 mg/day Study 302 [b]	Azathioprine Study 301	Placebo Study 302
Total enrolled	284	227	274	219	161	130
Sex, n (%)[b]						
Female	76 (27)	79 (35)	104 (38)	70 (30)	70 (43)[a]	39 (30)
Male	208 (73)	148 (65)	170 (62)	149 (68)	91 (57)	91 (70)
Ethnic origin, n (%)						
White	160 (56)	172 (76)	154 (56)	175 (80)	92 (57)	103 (79)
Black	63 (22)	26 (11)	62 (23)	27 (12)	41 (25)	13 (10)
Hispanic	48 (17)	6 (3)	42 (15)	7 (3)	15 (9)	3 (92)
Asian	7 (2)	10 (4)	1 (4)	2 (< 1)	10 (6)	4 (3)
Australian aborigine		3 (1)		1 (< 1)		
Other	6 (2)	10 (4)	6 (2)	7 (3)	3 (2)	7 (5)
Age (y)						
Mean	44.9	45.6	46.8	45.1	45.6	46.0
SD[c]	13.6	12.3	13.0	12.2	13.0	13.1
Minimum	16	15	13	17	12	16
Maximum	79	71	76	68	69	71

a: There were no statistically significant differences among treatment groups in any baseline characteristic in study 301, with the exception of sex ($p < 0.001$).

b: There were no statistically significant differences among treatment groups in any baseline characteristic in study 302.

c: SD = standard deviation.

TABLE 7.5B. DONOR SOURCE AND PRIMARY ETIOLOGY OF RENAL FAILURE OF PATIENTS ENROLLED IN STUDIES 301 AND 302[a]

Characteristic	Rapamune 2 mg/day Study 301	Rapamune 2 mg/day Study 302	Rapamune 5 mg/day Study 301	Rapamune 5 mg/day Study 302	Azathioprine Study 301	Placebo Study 302
Total enrolled	284	227	274	219	161	130
Donor source, n (%)						
Cadaver	180 (63)	173 (76)	167 (61)	174 (79)	119 (74)	99 (76)
Living unrelated donor	18 (6)	15 (7)	24 (9)	16 (7)	9 (6)	4 (3)
Living related donor	86 (30)	39 (17)	83 (30)	29 (13)	33 (20)	27 (21)
Primary etiology of renal failure, n (%)						
Autoimmune disease	13 (5)	7 (3)	7 (3)	8 (4)	13 (8)	5 (4)
Diabetes mellitus	59 (21)	28 (12)	53 (19)	34 (16)	32 (20)	17 (13)
Glomerulonephritis	64 (23)	65 (29)	50 (18)	51 (23)	18 (11)	32 (25)
Hypertension	72 (25)	35 (15)	77 (28)	27 (12)	47 (29)	2 (17)
IgA nephropathy (Berger's)	12 (4)	19 (8)	12 (4)	18 (8)	7 (4)	12 (9)
Interstitial nephritis/pyelonephritis	7 (2)	13 (6)	6 (2)	6 (3)	3 (2)	8 (6)
Obstructive uropathy/reflux	15 (5)	14 (6)	16 (6)	17 (8)	9 (6)	6 (5)
Other/unknown	19 (7)	23 (10)	21 (8)	25 (11)	13 (8)	10 (8)
Polycystic disease-kidney	23 (8)	23 (10)	32 (12)	33 (15)	19 (12)	18 (14)

a: There were no statistically significant differences among treatment groups in any baseline characteristic in either study.

7.6 Intent-to-Treat Primary Efficacy Analysis

7.6.1 Definition and Statistical Methods

The primary analysis of efficacy failure (the primary endpoint) for each study consisted of comparisons between each dose of Rapamune and the comparator done by using the Cochran-Mantel-Haenszel (CMH) statistic stratified by center. All patients assigned to treatment were included in this analysis. To maintain an overall probability of type I error of 0.05, comparisons of each dose of Rapamune with control therapy were made at the Bonferroni-corrected significance level of 0.025. If one treatment comparison was significant at the 0.025 level, thus preserving the overall error rate, then the other treatment comparison was assessed at the comparison-wise error rate of 0.05. The Breslow-Day statistic was used to test homogeneity of the treatment effect across the strata.

Because of differences in the relative days of patient follow-up visits, the 6-month efficacy evaluation occurred between 154 and 194 days after transplantation. A patient was defined as lost to follow-up if both of the following criteria were met: 1) the patient had no efficacy evaluation on or after the earliest possible 6-month visit (154 days); and 2) either the patient had an efficacy evaluation before the 6-month visit that confirmed absence of efficacy failure; or did not have an efficacy evaluation before to the 6-month visit. Patients defined as lost to follow-up were scored as efficacy failures, regardless of treatment assignment. In both pivotal trials the difference between discontinuation of the study treatment and discontinuation of follow-up was emphasized to participating investigators so that patients could be followed for efficacy over time, regardless of treatment.

The efficacy results of patients enrolled in centers with sparse enrollment were captured by pooling (collapsing) the data from noninformative centers and analyzing them as though they were from a single center. A center was defined as noninformative if it met one of the following criteria: 1) all of the patients enrolled by a single center had the same outcome (ie, all experienced efficacy failure or all did not); or 2) enrollment at a single center was so sparse that no patients were assigned to one of the treatments used in the analysis. For each efficacy analysis, all noninformative centers were combined into a single center. If the resulting center was still noninformative, then the informative center with the smallest number of patients was included in the combined center. In the case of ties, the

informative center with the highest incidence rate of efficacy failure for Rapamune was included.

7.6.2 Results of the Primary Intent-to-Treat Analysis of the Composite Endpoint (Efficacy Failure)

Table 7.6.2A shows that efficacy failure rates in both the Rapamune 2 mg/day treatment group (18.7%) and the Rapamune 5 mg/day treatment group (16.8%) were significantly lower than that in the azathioprine treatment group (32.3%; $p = 0.002$, $p < 0.001$, respectively). In study 302, the rates of efficacy failure in the Rapamune 2 mg/day (30.0%) and 5 mg/day (25.6%) treatment groups were significantly lower than that observed in the placebo group (47.7%); [$p = 0.002$, $p < 0.001$, respectively].

TABLE 7.6.2A . PRIMARY INTENT-TO-TREAT ANALYSES OF THE COMPOSITE PRIMARY ENDPOINT (EFFICACY FAILURE) FOR STUDIES 301 AND 302; NUMBER (%)

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
	301	302	301	302	301	302
Variable	(n = 284)	(n = 227)	(n = 274)	(n = 219)	(n = 161)	(n = 130)
Efficacy failure at 6 months[a]	53 (18.7)	68 (30.0)	46 (16.8)	56 (25.6)	52 (32.3)	62 (47.7)
CMH p-value[b]	0.002	0.002	< 0.001	< 0.001		
Breslow-Day p-value[b]	0.290	0.169	0.310	0.375		
Components of efficacy failure						
Biopsy-proven acute rejection[c]	47 (16.6)	56 (24.7)	31 (11.3)	42 (19.2)	47 (29.2)	54 (41.5)
Graft loss[c,d]	3 (1.1)	7 (3.1)	8 (2.9)	8 (3.7)	4 (2.5)	5 (3.9)
Death[c]	2 (0.7)	5 (2.2)	5 (1.8)	6 (2.7)	0	3 (2.3)
Lost to follow-up[e]	1 (0.4)	0	2 (0.7)	0	1 (0.6)	0

a: The primary endpoint is a composite consisting of the first occurrence of acute biopsy-confirmed rejection, graft loss, or death.

b: CMH p-values for comparison of each dose of Rapamune to comparator, stratified by center. All comparisons were made to azathioprine in study 301; similarly, all comparisons were made to placebo in study 302. The Bonferroni-corrected level of significance was used to control the experiment-wise error rate for each protocol. Breslow-Day p-values were tests of consistency of the treatment effect across the stratification (centers). All patients randomly assigned to treatment were included in this analysis.

c: Individual components of the primary endpoint sum to primary endpoint.

d: Graft loss defined as functional or physical loss.

e: Patients lost to follow-up were scored as efficacy failure, regardless of treatment.

7.7 Stratified Analyses of the Composite Endpoint (Efficacy Failure)

The CMH analysis of the rate of efficacy failure stratified by race (black or non-black) in study 301 and by donor source in study 302 further supported the significant treatment differences seen in the primary efficacy analysis (Tables 7.7A and 7.7B).

The efficacy results were not consistent across the race strata in the comparison of Rapamune 2 mg/day to azathioprine: the rate of efficacy failure for non-black patients was lower for those receiving Rapamune 2 mg/day (14.0%) than for those non-black patients receiving azathioprine (31.9%) but the efficacy failure rate for black patients in the Rapamune 2 mg/day group was higher (34.9%) than for black patients in the azathioprine group (33.3%). It is this reversal in the observed favorable effect for black patients (Rapamune 2 mg/day vs azathioprine) that is underscored by the statistically significant Breslow Day test. No such reversal of treatment effect was observed for the patients in the Rapamune 5 mg/day treatment group, where black and non-black patients had lower rates of efficacy failure (18.0% and 16.4%, respectively) when compared with black and non-black patients in the azathioprine group (33.3% and 31.9%, respectively).

TABLE 7.7A. ANALYSIS OF THE COMPOSITE ENDPONT (EFFICACY FAILURE) AT 6 MONTHS STRATIFED BY RACE: STUDY 301; NUMBER (%)

Variable	Rapamune 2 mg/day n = 284	Rapamune 5 mg/day n = 274	Azathioprine n = 161
Overall rate, No. (%)	53 (18.7)	46 (16.8)	52 (32.3)
Black (n = 166)	22/63 (34.9)	11/61 (18.0)	14/42 (33.3)
Non-black (n = 553)	31/221 (14.0)	35/213 (16.4)	38/119 (31.9)
CMH p-value[a]	0.002	< 0.001	
Breslow-Day p-value	0.024	0.928	

a: Overall.

The efficacy results were not consistent across the donor strata in the comparisons of Rapamune 2 mg/day or 5 mg/day to placebo (study 302). Treatment with Rapamune conferred a larger treatment advantage in patients who received an allograft from a living donor than those who received an allograft from a cadaveric donor. The efficacy failure rate of 61.3% among patients who received an allograft from a living donor and who were randomized to the placebo group is higher than would be expected; this may due to the small number of patients in this stratum.

TABLE 7.7B. ANALYSIS OF EFFICACY FAILURE AT 6 MONTHS STRATIFIED BY DONOR ORIGIN: STUDY-302-GL; NUMBER (%)

Variable	Rapamune 2 mg/day n = 227	Rapamune 5 mg/day n = 219	Placebo n = 130
Overall rate, No. (%)	68 (30.0)	56 (25.6)	62 (47.7)
Cadaver (n = 447)	55/174 (31.6)	48/174 (27.6)	43/99 (43.4)
Living (n = 129)	13/53 (24.5)	8/45 (17.8)	19/31 (61.3)
CMH p-value[a]	< 0.001	< 0.001	
Breslow-Day p-value	0.050	0.029	

a: Overall.

7.7.1 Results of Intent-to-Treat Analysis of Efficacy Failure in Demographic Subpopulations

Tables 7.7.1A and 7.7.1B show the rates of the primary endpoint of efficacy failure by treatment group in selected subgroups of the patients in studies 301 and 302, respectively.

TABLE 7.7.1A. INCIDENCE RATES OF EFFICACY FAILURE 6 MONTHS AFTER TRANSPLANTATION IN SELECTED SUBGROUPS OF PATIENTS IN STUDY 301: NUMBER (%) OF PATIENTS

Subgroup	Rapamune 2 mg/day (n = 284)	Rapamune 5 mg/day (n = 274)	Azathioprine (n = 161)
Sex			
Male	39/208 (18.8)[c]	26/171 (15.2)[c]	35/90 (38.9)
Female	14/76 (18.4)	20/103 (19.4)	17/71 (23.9)
Ethnic Origin			
Black	22/63 (34.9)	11/61 (18.0)	14/42 (33.3)
Hispanic	8/48 (16.7)	6/43 (14.0)	5/14 (35.7)
Oriental (Asian)	1/7 (14.3)	1/10 (10.0)	2/10 (20.0)
White	22/160 (13.8)[c]	27/154 (17.5)[b]	31/92 (33.7)
Other	0/6 (0)	1/6 (16.7)	0/3 (0)
Age			
Under 18 years	0/3 (0)	0/2 (0)	0/3 (0)
18 to 65 years	48/260 (18.5)[c]	42/257 (16.3)[c]	51/153 (33.3)
Over 65 years	5/21 (23.8)	4/15 (26.7)	1/5 (20.0)
Number of HLA-mismatches[d]			
0-3 mismatches	25/155 (16.1)[a]	18/140 (12.9)[b]	23/82 (28.1)
4-6 mismatches	28/126 (22.2)[a]	28/132 (21.2)[a]	29/79 (36.7)

a-c: Treatment differences of each dose of Rapamune to azathioprine were determined separately with Fisher's exact test. Statistical significance at less than the 0.05, 0.01, and 0.001 levels were denoted with the superscripted letters a, b, and c, respectively.

d: The number of HLA-mismatches was not collected for 5 patients; these patients were excluded from this analysis.

TABLE 7.7.1B. INCIDENCE RATES OF EFFICACY FAILURE 6 MONTHS AFTER TRANSPLANTATION IN SELECTED SUBGROUPS OF PATIENTS IN STUDY 302: NUMBER (%) OF PATIENTS

Subgroup	Rapamune 2 mg/day (n = 227)	Rapamune 5 mg/day (n = 219)	Placebo (n = 130)
Sex			
Male	41/148 (27.7)[c]	35/149 (23.5)[c]	46/91 (50.6)
Female	27/79 (34.2)	21/70 (30.0)	16/39 (41.0)
Ethnic Origin			
Australian Aborigine	0/3 (0)	1/1(100.0)	-
Black	8/26 (30.8)	9/27 (33.3)	5/13 (38.5)
Hispanic	1/6 (16.7)	1/2 (50.0)	2/4 (50.0)
Oriental (Asian)	5/10 (50.0)	2/7 (28.6)	2/3 (66.7)
White	49/172 (28.5)[b]	40/175 (22.9)[c]	48/103 (46.6)
Other	5/10 (50.0)	3/7 (42.9)	5/7 (71.4)
Age			
Under 18 years	0/1 (0)	0/1 (0)	0/1 (0)
18 to 65 years	66/220 (30.0)[c]	56/215 (26.1)[c]	59/122 (48.4)
Over 65 years	2/6 (33.3)	0/3 (0)	3/7 (42.9)
Number of HLA-mismatches			
0-3 mismatches	28/110 (25.5)	22/108 (20.4)[a]	26/68 (38.2)
4-6 mismatches	40/117 (34.2)[b]	34/111 (30.6)[c]	36/62 (58.1)

a-c: Treatment differences of each dose of Rapamune to placebo were determined separately with Fisher's exact test. Statistical significance at less than the 0.05, 0.01, and 0.001 levels were denoted with the superscripted letters a, b, and c, respectively.

For both studies, significantly lower efficacy failure rates were observed at 6 months in both Rapamune treatment groups than in the respective control group for the following subgroups of patients: male patients, white patients, patients between 18 and 65 years of age and those with 4-6 HLA-mismatches. In study 301, significantly lower efficacy failure rates were also seen in the Rapamune-treated groups than in the azathioprine-treated group for patients with 0-3 HLA mismatches; however, in study 302 only patients in the Rapamune 5 mg/day group with 0-3 mismatches had significantly lower efficacy failure rates compared with placebo. In addition, patients with 0-3 HLA mismatches in the Rapamune 2 mg/day group had numerically lower efficacy failure rates than those in the placebo group.

Comparison of the incidence of efficacy failure among the remaining subgroups of patients did not demonstrate significant differences between the active treatment and control groups:

- In study 301, the rates of efficacy failure for female patients were low: less than 20% in both Rapamune dose groups and 23.9% in the azathioprine group. In

study 302, the rate of efficacy failure for female patients was higher than in study 301 in all treatment groups, numerically higher than in the male patients, but lower numerically lower than in the placebo group.

- Black patients in study 301 had a numerically lower efficacy failure rate in the Rapamune 5 mg/day group (18%) than in either the Rapamune 2 mg/day group (34.9%) or the azathioprine group (33.3%), although the differences were not statistically different. Fewer black patients were enrolled in study 302; the rates of efficacy failure were greater than 30% in all treatment groups.

- The efficacy failure rates for Hispanic patients were lower in the Rapamune groups (study 301 only) than in either control group, though the differences did not reach statistical significance.

- The subgroup analyses for age (patients less than 18 years or older than 65 years) and ethnic origin (Australian aborigines and Asian patients in both studies, and Hispanic patients in study 302 only) were not informative because of the small numbers of patients.

7.8 Patient and Graft Survival One Year After Transplantation

7.8.1 Results of Analysis of One-Year Patient Survival

Table 7.8.1A shows a summary tabulation of patient survival 1 year after transplantation for each study by treatment group. One-year patient survival rates were 97.2% and 96.0% in the Rapamune 2 mg/day groups and 96.5% and 95.0% in the Rapamune 5 mg/day groups (studies 301 and 302, respectively). All treatment groups, including azathioprine and placebo, had excellent rates of one-year patient survival.

TABLE 7.8.1A. SUMMARY TABULATION OF PATIENT SURVIVAL ONE YEAR AFTER TRANSPLANTATION (STUDIES 301 AND 302); NUMBER (%)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
Patient survival, n (%)	276 (97.2)	219 (96.5)	263 (96.0)	208 (95.0)	158 (98.1)	123 (94.6)
Patient death, n (%)	8 (2.8)	8 (3.5)	11 (4.0)	11 (5.0)	3 (1.9)	7 (5.4)
Fisher's exact p-value	0.753	0.420	0.271	1.0		
Relative risk [a]	1.51	0.65	2.16	0.93		
(95% CI)	(0.41 to 5.62)	(0.24 to 1.76)	(0.61 to 7.61)	(0.37 to 2.35)		
Difference in rates [b]	-1.0	1.9	-2.2	0.4		
(95% CI)	(-3.8 to 1.9)	(-2.7 to 6.4)	(-5.3 to 1.0)	(-4.5 to 5.2)		

a: The relative risk (RR) of patient death is a ratio of the probability of patient death for Rapamune over the corresponding probability for the comparator. A 95% CI of the RR that contains 1 supports the null hypothesis of no difference in treatment.

b: The difference in rates was calculated as the rate of patient survival in the Rapamune group minus the corresponding rate for the comparator. A 95% CI of the difference in rates that contains 0 supports the null hypothesis of no difference in treatment.

7.8.2 Results of The Analysis of One-Year Graft Survival

Table 7.8.2A shows a summary tabulation of graft survival 1 year after transplantation for each study by treatment group. There were no significant differences between treatment groups in graft survival through 1 year in either study 301 or 302. Graft survival rates were at or above 89.9% in each of the Rapamune-treated groups. Patients who died with functioning grafts accounted for approximately 40% of graft losses in the Rapamune groups during first 6 months after transplantation.

TABLE 7.8.2A. SUMMARY TABULATION OF GRAFT SURVIVAL ONE YEAR AFTER TRANSPLANTATION (STUDIES 301 AND 302); NUMBER (%)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
Graft survival, n (%)	269 (94.7)	204 (89.9)	254 (92.7)	199 (90.9)	151 (93.8)	114 (87.7)
Graft loss, n (%)	8 (2.8)	15 (6.6)	12 (4.4)	11 (5.0)	8 (5.0)	9 (6.9)
Patient death, n (%)	7 (2.5)	8 (3.5)	8 (2.9)	9 (4.1)	2 (1.2)	7 (5.4)
Fisher's exact p-value	0.674	0.597	0.845	0.366		
Relative risk [a]	0.85	0.82	1.18	0.74		
(95% CI)	(0.39 to 1.85)	(0.45 to 1.50)	(0.56 to 2.45)	(0.40 to 1.38)		
Difference in rates [b]	0.9	2.2	-1.1	3.2		
(95% CI)	(-3.6 to 5.5)	(-4.7 to 9.1)	(-5.9 to 3.8)	(-3.7 to 10.0)		

a: The relative risk (RR) of graft loss is a ratio of the probability of graft loss for Rapamune over the corresponding probability for the comparator. A 95% CI of the RR that contains 1 supports the null hypothesis of no difference treatment.

b: The difference in rates was calculated as the rate of graft survival in the Rapamune group minus the corresponding rate for the comparator. A 95% CI of the difference in rates that contains 0 supports the null hypothesis of no difference in treatment.

7.9 Analysis of Treatment Failure

Treatment failure was defined as the first occurrence of biopsy-proven acute rejection or premature discontinuation of the study treatment for any reason within the first 6 months after transplantation. The incidence of treatment failure, stratified by center, was analyzed in the same manner as the primary efficacy analysis.

Table 7.9A shows an analysis by treatment group of the rate of treatment failure (defined as the first occurrence of biopsy-proven acute rejection or premature discontinuation of study medication for any reason during the first 6 months after transplantation) by treatment group.

In both studies 301 and 302, the rate of treatment failure for Rapamune 2 mg/day (36.3%, $p = 0.006$ and 41.4%, $p = 0.002$, respectively) was significantly lower than in either the azathioprine (49.1%) or placebo (60.0%) groups. Additionally, both studies 301 and 302 demonstrated lower rates of treatment failure for Rapamune 5 mg/day (38.7%, $p = 0.071$ and 46.1%, $p = 0.013$) when compared to either azathioprine (49.1%) or placebo (60.0%). This analysis supports the conclusion that improvement in biopsy-confirmed acute rejection rates for the Rapamune 2 mg/day group was not biased by early withdrawal of patients for reasons other than acute rejection. In contrast, treatment failure was not significantly lower in the Rapamune 5 mg/day group in study 301 compared to controls. Although the rates of discontinuation for biopsy-confirmed acute rejection were lower in the Rapamune 5 mg/day groups, the rates of discontinuation for any other reason were higher, suggesting that this dose level may not be as well tolerated.

TABLE 7.9A. ANALYSIS OF RATE OF TREATMENT FAILURE (% OF PATIENTS) 6 MONTHS AFTER TRANSPLANTATION (STUDIES 301 AND 302)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
Treatment failure at 6 months[a]	103 (36.3)	94 (41.4)	106 (38.7)	101 (46.1)	79 (49.1)	78 (60.0)
CMH p-value[b]	0.006	0.002	0.071	0.013		
Breslow-Day p-value[b]	0.458	0.783	0.812	0.538		
Components of treatment failure[c] n, (%)						
Biopsy-proven acute rejection	38 (13.4)	48 (21.1)	20 (7.3)	35 (16.0)	40 (24.8)	48 (36.9)
Discontinuation	65 (22.9)	46 (20.3)	86 (31.4)	66 (30.1)	39 (24.2)	30 (23.1)

a: Treatment failure is defined as the first occurrence of biopsy-proven acute rejection or premature discontinuation from study medication for any reason within the first 6 months of the study.

b: CMH p-values are for the comparison of each dose of Rapamune to comparator while stratifying by center. All comparisons were made to azathioprine in study 301; similarly, all comparisons were made to placebo in study 302. The Bonferroni-corrected level of significance (0.025) was used to control the experiment-wise error rate for each protocol. Breslow-Day p-values tested consistency of the treatment effect across the stratification (centers). All patients randomly assigned to treatment were included in this analysis.

c: Individual components sum to total number of treatment failures.

7.10 Analyses of Acute Rejection

7.10.1 Definitions

Several analyses of the acute rejection endpoints were performed. These include: 1) intent-to-treat analysis of the rates of first biopsy-confirmed acute rejection episodes; 2) intent-to-treat analysis of the rates of any first presumed acute rejection episode (defined below); and 3) intent-to-treat analysis of any (biopsy-confirmed plus presumed) first acute rejection episode (defined below).

Since not all acute rejections episodes were confirmed by local biopsy (either the patient was treated for rejection without a biopsy or the patient was presumed to have acute rejection but biopsy results were not interpreted as acute rejection), it was important to assess treatment differences for all acute rejections because the endpoints were representative of medical practice. Acute rejections, therefore, were categorized into the following mutually exclusive groups.

1. Biopsy-confirmed acute rejection episodes were defined as acute rejection episodes confirmed by local biopsy without regard to treatment for acute rejection. The diagnosis and graded severity of acute rejection were made using the Banff criteria.

2. Presumed acute rejections were defined as clinically diagnosed acute rejection episodes that were treated by the physician, but either a local biopsy did not indicate an acute rejection or a local biopsy was not performed at all.

7.10.2 Results of the Intent-to-Treat Analysis of the First Biopsy-Confirmed Acute Rejection Episodes

Table 7.10.2A shows the results of the analysis of the first occurrence of biopsy-confirmed acute rejection in the phase III studies (studies 301 and 302). In study 301, the rates of biopsy-confirmed acute rejection in both the Rapamune 2 mg/day treatment group (16.9%) and the Rapamune 5 mg/day treatment group (12.0%) were significantly lower ($p = 0.002$ and $p < 0.001$, respectively) than the rate in the azathioprine treatment group (29.8%). In study 302, there was also a significant decrease in the rate of first biopsy-confirmed acute rejection in the Rapamune 2 mg/day treatment group (24.7%) and the Rapamune 5 mg/day treatment group (19.2%) compared to 41.5% in the placebo group ($p < 0.001$ for both comparisons). Each analysis of the first biopsy-confirmed acute rejection was consistent across the centers, as evidenced by the nonsignificant Breslow-Day p-values.

Each study showed that the addition of Rapamune (2 mg/day or 5 mg/day) to CsA/corticosteroid therapy significantly reduced the incidence of biopsy-confirmed acute rejection during the first 6 months following transplantation.

TABLE 7.10.2A. INTENT-TO-TREAT ANALYSIS OF THE RATE (% OF PATIENTS) OF THE FIRST BIOPSY-CONFIRMED ACUTE REJECTION[a] BY TREATMENT GROUP AT 6 MONTHS IN STUDIES 301 AND 302

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
Biopsy-confirmed acute rejections at 6 months, n (%)	48 (16.9)	56 (24.7)	33 (12.0)	42 (19.2)	48 (29.8)	54 (41.5)
CMH p-value[b]	0.002	0.003	< 0.001	< 0.001		
Breslow-Day p-value[b]	0.471	0.453	0.431	0.121		
Components, n (%)						
Biopsy-confirmed acute rejections	47 (16.6)	56 (24.7)	31 (11.3)[c]	42 (19.2)	47 (29.2)	54 (41.5)
Patients lost to follow-up[d]	1 (0.4)	0	2 (0.7)	0	1 (0.6)	0

a: The acute rejection component was defined as any biopsy-confirmed rejection (grade 1 or higher by Banff criteria read by the local pathologist) regardless of treatment for rejection.

b: CMH p-values are for the comparison of each dose of Rapamune to comparator, stratified by center. All comparisons were made to azathioprine in study 301; similarly, all comparisons were made to placebo in study 302. The Bonferroni-corrected level of significance (0.025) was used to control the experiment-wise error rate for each protocol. Breslow-Day p-values tested consistency of the treatment effect across the stratification (centers). All patients randomly assigned to treatment were included in this analysis.

c: One patient in this treatment group was included in the primary efficacy analysis as a protocol-defined functional graft loss. However, the patient actually recovered and subsequently had a biopsy-confirmed acute rejection episode. Thus, this patient was defined as having an endpoint of an acute rejection in this analysis.

d: Patients lost to follow-up were scored as acute rejection, regardless of treatment.

7.10.3 Results of the Intent-to-Treat Analysis of the First of Any (Biopsy-Confirmed Plus Presumed) Acute Rejection Episodes

Table 7.10.3A shows an analysis of all (biopsy-confirmed and presumed) acute rejection episodes by treatment group. In this analysis there was a significant reduction in the acute rejection rate in both studies (studies 301 and 302) for both Rapamune treatment groups (Rapamune 2 mg/day and 5 mg/day), further supporting the positive treatment effects of Rapamune compared with those of azathioprine or placebo. Rates of presumed rejection were similar between treatment groups; the results of this analysis were largely driven by the biopsy-confirmed acute rejection component.

TABLE 7.10.3A. INTENT-TO-TREAT ANALYSIS OF ALL (BIOPSY-CONFIRMED AND PRESUMED) ACUTE REJECTION EPISODES AT 6 MONTHS; NUMBER (%)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
All first acute rejections at 6 months, n (%)	72 (25.4)	75 (33.0)	54 (19.7)	60 (27.4)	58 (36.0)	67 (51.5)
CMH p-value[a]	0.009	0.004	< 0.001	< 0.001		
Breslow-Day p-value[a]	0.446	0.645	0.191	0.187		
Components, n (%)						
Biopsy-confirmed acute rejections	48 (16.9)	56 (24.4)	33(12.0)[b]	43 (19.6)	47 (29.2)	54 (41.5)
Presumed acute rejections	23 (8.1)	19 (8.4)	19 (6.9)	17 (7.8)	10 (6.2)	13 (10.0)
Patients lost to follow-up[b]	1 (0.4)	0	2 (0.7)	0	1 (0.6)	0

a: CMH p-values are for the comparisons of each dose of Rapamune to comparator, stratified by center. All comparisons were made to azathioprine in study 301; similarly, all comparisons were made to placebo in study 302. The Bonferroni-corrected level of significance (0.025) was used to control the experiment-wise error rate for each protocol. Breslow-Day p-values tested consistency of the treatment effect across the stratification (centers). All patients randomly assigned to treatment were included in this analysis.

b: Patients lost to follow-up were scored as acute rejection, regardless of treatment.

7.10.4 Results of Analysis of Histologic Grade of First Biopsy-Confirmed Acute Rejection (Studies 301 and 302)

Table 7.10.4A shows the Banff histological grade by treatment group of the first biopsy-confirmed acute rejection at 6 months for patients who had biopsy-confirmed acute rejection in the phase III studies.

TABLE 7.10.4A. ANALYSIS OF HISTOLOGICAL GRADE[a] OF FIRST BIOPSY-CONFIRMED ACUTE REJECTION AT 6 MONTHS; NUMBER (%)

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
	301	302	301	302	301	302
Variable	(n = 47)	(n = 56)	(n = 31)	(n = 42)	(n = 47)	(n = 54)
Histological Grade, n (%)						
Grade I (mild)	21 (44.7)	28 (50.0)	19 (61.3)	24 (57.1)	19 (40.4)	21 (38.9)
Grade II (moderate)	19 (40.4)	24 (42.9)	8 (25.8)	17 (40.5)	23 (48.9)	29 (53.7)
Grade III (severe)	7 (14.9)	4 (7.1)	4 (12.9)	1 (2.4)	5 (10.6)	4 (7.4)
Row mean score p-value[b]	1.000[c]	0.335[d]	0.241[e]	0.056[f]		

a: As defined by the Banff criteria.
b: The row mean score test indicates the distribution of severities and the treatment differences of these ordered severities, assessed through a test of the row mean scores, an option of the FREQ Procedure of SAS.
c: p-value for comparison of Rapamune 2 mg/day with azathioprine = 1.000.
d: p-value for comparison of Rapamune 2 mg/day with placebo = 0.335.
e: p-value for comparison of Rapamune 5 mg/day with azathioprine = 0.241.
f: p-value for comparison of Rapamune 5 mg/day with placebo = 0.056.

An additional post-hoc analysis was performed to account for all patients assigned to treatment; the results are presented in Table 7.10.4B. In this analysis, each patient was assigned an outcome: Patients who did not have efficacy failure were categorized as "none," patients who had an episode of biopsy-confirmed acute rejection were divided into subgroups by histologic severity, and patients who had an outcome of graft loss, death, or lost to follow-up were categorized as "other." The data from each study show more favorable response patterns for the Rapamune treatment groups suggesting fewer and/or less severe endpoints than in the azathioprine or placebo treatment groups.

TABLE 7.10.4B. INTENT-TO-TREAT ANALYSIS OF THE INCIDENCE OF FIRST BIOPSY-CONFIRMED ACUTE REJECTION BY HISTOLOGICAL GRADE OF SEVERITY: STUDIES 301 AND 302; NUMBER (%)

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
Patient outcome, n (%)	301 (n = 284)	302 (n = 227)	301 (n = 274)	302 (n = 219)	301 (n = 161)	302 (n = 130)
None[a]	231 (81.3)	159 (70.0)	228 (83.2)	163 (74.4)	109 (67.7)	68 (52.3)
Grade I (mild)[b]	21 (7.4)	28 (12.3)	19 (6.9)	24 (11.0)	19 (11.8)	21 (16.3)
Grade II (moderate)[b]	19 (6.7)	24 (10.6)	8 (2.9)	17 (7.8)	23 (14.3)	29 (22.3)
Grade III (severe)[b]	7 (2.5)	4 (1.8)	4 (1.5)	1 (0.5)	5 (3.1)	4 (3.1)
Other[c]	6 (2.1)	12 (5.3)	15 (5.5)	14 (6.4)	5 (3.1)	8 (6.1)
Row mean score p-value[h]	0.006[d]	0.006[e]	0.025[f]	0.001[g]		

a: Includes patients who did not have any component of efficacy failure (biopsy-confirmed acute rejection, graft loss, death, or lost to follow-up).
b: As defined by the Banff criteria.
c: Includes patients who proceeded directly to an outcome of graft loss or death; or who were lost to follow-up.
d: p-Value for comparison of Rapamune 2 mg/day with azathioprine = 0.006.
e: p-Value for comparison of Rapamune 2 mg/day with placebo = 0.006.
f: p-Value for comparison of Rapamune 5 mg/day with azathioprine = 0.025.
g: p-Value for comparison of Rapamune 5 mg/day with placebo = 0.001.
h: The row mean score test examines the distribution of severities and tests treatment differences of these ordered severities, assessed through a test of the row mean scores (an option of the FREQ Procedure of SAS). The overall p-value for study 301, p=0.029; study 302, p=0.003.

7.10.5 Results of Analysis of the Use of Anti-T Lymphocyte Therapies to Treat the First Biopsy-Confirmed Acute Rejection Episode

Table 7.10.5A shows the use in each treatment group of antibody therapies to treat the first biopsy-confirmed acute rejection episode during the first 6 months after transplantation. The data suggest that there was significantly less use of anti-T lymphocyte antibody therapies to treat first biopsy-confirmed, acute rejection in the Rapamune 5 mg/day (studies 301 and 302) and Rapamune 2 mg/day (study 301) groups than in the control groups. Additionally, there was an observable decrease in the use of antibody therapies in patients receiving Rapamune 2 mg/day in study 302 compared to placebo.

TABLE 7.10.5A. NUMBER (%) OF PATIENTS ADMINISTERED ANTIBODY THERAPIES TO TREAT THE FIRST BIOPSY-CONFIRMED ACUTE REJECTION EPISODE (STUDIES 301 AND 302)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 2 mg/day 302 (n = 227)	Rapamune 5 mg/day 301 (n = 274)	Rapamune 5 mg/day 302 (n = 219)	Azathioprine 301 (n = 161)	Placebo 302 (n = 130)
Number of Patients, n (%)	16 (5.6)	9 (4.0)	8 (2.9)	7 (3.2)	20 (12.4)	11 (8.5)
Lower 95% CI, %	3.2	1.8	1.3	1.3	7.8	4.3
Upper 95% CI, %	9.0	7.4	5.7	6.5	18.5	14.6
Fisher's exact p-value[a]	0.017	0.094	< 0.001	0.044		

a: Fisher's exact p-values compare each dose of Rapamune to comparator. All comparisons were made to azathioprine in study 301; similarly, all comparisons were made to placebo in study 302. The Bonferroni-corrected level of significance was 0.025 for each protocol. All patients assigned to treatment were included in this analysis.

7.10.6 Analysis of Acute Rejection as a Predictor of 12-Month Graft Loss (Studies 301 and 302)

The results of the pooled analysis of the concordance between the occurrence of biopsy-confirmed acute rejection within 6 months after transplantation and an outcome of graft loss during the first year after transplantation suggested that an endpoint of biopsy-confirmed acute rejection within the first 6 months after transplantation had predictive value in terms of 1-year graft survival. Table 7.10.6A shows overall concordance between the biopsy-confirmed acute rejection at 6 months and 12-month graft survival.

TABLE 7.10.6A. BIOPSY-CONFIRMED ACUTE REJECTION AT 6 MONTHS AS A PREDICTOR OF 12-MONTH GRAFT SURVIVAL; NUMBER (%)

Biopsy-confirmed Acute Rejection by 6 months	Graft Loss[a] by 12 months Yes	No
Yes (n = 281)	27 (9.6)	254 (90.4)
No (n = 1014)	36 (3.5)	978 (96.5)

a: The relative risk of having a graft loss by 12 months if biopsy-confirmed acute rejection occurred before 6 months was 2.71 (95% CI, 1.67 - 4.38)

Table 7.10.6B summarizes the concordance between biopsy-confirmed acute rejection at 6 months and 12-month graft survival by treatment group.

TABLE 7.10.6. RELATIVE RISK OF GRAFT LOSS AT 12 MONTHS IN PATIENTS EXPERIENCING ACUTE REJECTION AT 6 MONTHS

Treatment Group	Relative Risk of Graft Loss[a]	95% confidence interval
Rapamune 2 mg/day	2.52	1.12 - 5.65
Rapamune 5 mg/day	4.22	1.92 - 9.28
Azathioprine	2.43	0.63 - 9.93
Placebo	1.12	0.32 - 4.00

a: In patients experiencing acute rejection at 6 months.

7.10.7 Efficacy Analyses of a Subpopulation of Patients Considered to be at High Risk for Acute Rejection

7.10.7.1 Background

Renal transplant patients who, in general, are considered to be at high risk for acute rejection include, but may not be limited to: African American patients (black patients), those receiving second or third transplants or those with high levels of pre-formed antibody (ie, high panel reactive antibodies), and those with high degrees of HLA mismatch. However, study 301, because of its design (prospective, stratified by race [black or non-black], targeted sample size of 600 patients, and limited to centers in the United States), afforded a unique opportunity to prospectively compare the effect of two doses of Rapamune to azathioprine in black patients. This study also permitted a dose-concentration/effect analysis to be performed in this population. The efficacy data from study 301 for this subpopulation will be reviewed in the following sections.

7.10.7.2 Pharmacokinetics of CsA and Rapamune in Black Patients

Despite the administration of higher daily doses of CsA to achieve trough concentrations comparable to non-black patients (Table 7.10.7.2A) there were no statistically significant differences in actual whole blood trough CsA concentrations with respect to Rapamune dose group ($p = 0.67$) or race ($p = 0.72$) [Table 7.10.7.2B]. A comparison of dose-normalized whole blood trough CsA concentrations showed significant differences with respect to race ($p = 0.03$); dose-normalized whole blood trough CsA concentrations for black patients were significantly lower than those of non-black patients, which is consistent with the larger doses required in black patients.

TABLE 7.10.7.2A. MEAN CYCLOSPORINE DOSES (mg) OVER TIME BY RACE AND TREATMENT GROUP (STUDY 301)

Treatment	Race	Month 1	Months 2 - 3	Months 4 - 6
Rapamune placebo[a]	Non-black	594 (27.6)[b]	490 (33.5)	390 (33.6)
	Black	622 (37.2)	530 (32.4)	464 (31.7)
	Overall	601 (30.5)	501 (33.3)	409 (33.9)
Rapamune 2 mg/day	Non-black	560 (30.5)	423 (35.3)	354 (34.5)
	Black	598 (32.0)	474 (33.6)	409 (36.2)
	Overall	568 (30.9)	432 (35.2)	364 (35.3)
Rapamune 5 mg/day	Non-black	525 (29.2)	395 (37.8)	336 (35.9)
	Black	542 (29.2)	465 (41.1)	371 (43.3)
	Overall	528 (29.2)	410 (39.4)	343 (38.0)

a: These patients received azathioprine as well as Rapamune placebo.
b: Intersubject %CVs.

TABLE 7.10.7.2B. AVERAGE TROUGH WHOLE BLOOD CYCLOSPORINE CONCENTRATIONS OVER TIME IN RENAL ALLOGRAFT RECIPIENTS[a] (STUDY 301)

		Month 1		Months 2 - 3		Months 4 - 6	
Treatment	Race	n	ng/mL (%CV[b])	n	ng/mL (%CV[b])	n	ng/mL (%CV[b])
Rapamune 2 mg/day	Non-black	81	361 (41.7/31.2)	117	317 (45.4/26.5)	145	267 (33.7/28.6)
	Black	19	367 (37.0/37.5)	29	324 (37.8/33.8)	29	268 (35.2/32.1)
	Overall	100	363 (40.7/32.4)	146	319 (43.8/27.9)	174	268 (33.8/29.2)
Rapamune 5 mg/day	Non-black	69	350 (53.3/30.9)	93	302 (33.6/26.3)	128	247 (34.6/23.6)
	Black	23	403 (46.5/40.0)	33	287 (38.4/27.5)	37	259 (31.5/27.4)
	Overall	92	363 (51.5/33.2)	126	298 (34.8/26.7)	165	250 (33.8/24.5)
Rapamune Placebo[c]	Non-black	51	358 (36.4/33.9)	43	314 (24.0/24.7)	59	253 (25.3/17.2)
	Black	17	438 (56.0/36.3)	20	292 (23.7/25.4)	22	278 (27.5/22.1)
	Overall	68	378 (44.4/34.5	63	307 (24.0/24.9)	81	260 (26.2/18.6)

Trough Concentration	Source of Variation	p-value from ANOVA
Actual	Treatment	0.67
	Race	0.72
	Interval	0.001
Normalized[d]	Treatment	0.02
	Race	0.03
	Interval	0.001

a: Mean of average troughs (by area method) across days in individual patients.
b: Intersubject/intrasubject %CVs.
c: These patients received azathioprine and Rapamune placebo.
d: Individual trough concentrations were normalized to 100 mg prior to ANOVA.

Unlike CsA, mean doses for the Rapamune 2 mg/day group remained constant over the 205 day period, while mean doses for the Rapamune 5 mg/day group declined slightly over approximately the initial 60-days following transplantation before attaining plateau levels. The average Rapamune doses were summarized by treatment group and race. ANOVA showed an expected difference by treatment group but not by race, indicating that Rapamune, unlike CsA, does not require higher dosing in black patients. This is supported by the statistical analysis of the whole blood Rapamune pharmacokinetic parameters which showed that there were no statistically significant differences for any of the parameters with respect to either treatment group or month or race. Table 7.10.7.2C provides a summary of the whole blood Rapamune pharmacokinetic parameters for the 2 mg/day and 5 mg/day treatment groups.

TABLE 7.10.7.2C. WHOLE BLOOD RAPAMUNE PHARMACOKINETIC PARAMETERS IN POST-TRANSPLANT PATIENTS (STUDY 301)

Treatment	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$ (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
Rapamune 2 mg/day (n = 19)	12.2 ± 6.2[a,b] (51.1/23.2)	3.01 ± 2.40 (79.6/45.5)	158 ± 70 (44.1/23.5)	182 ± 72 (39.7/20.3)
Rapamune 5 mg/day (n = 23)	37.4 ± 21 (56.2/43.6)	1.84 ± 1.30 (70.4/46.3)	396 ± 193 (48.7/40.8)	221 ± 143 (64.7/31.6)
Source of Variability	p-values from ANOVA[c]			
Treatment	0.14	0.14	0.38	0.27
Race	0.17	0.41	0.13	0.12
Month	0.50	0.98	0.42	0.74

a: Data presented as the mean ± SD (intersubject/intrasubject %CVs).
b: The overall averages among subjects include the average value in each patient over time.
c: $C_{max,ss}$, and $AUC_{\tau,ss}$ were normalized to a 2 mg/day dose prior to ANOVA.
d: CL/F/WT = oral dose clearance adjusted by weight.

Average whole blood Rapamune concentrations were similar between black and non-black patients within treatment groups (Table 7.10.7.2D). There is an expected increase in the average trough level in black patients when Rapamune 5 mg/day is administered.

TABLE 7.10.7.2D. AVERAGE TROUGH WHOLE BLOOD RAPAMUNE CONCENTRATIONS OVER TIME IN RENAL ALLOGRAFT RECIPIENTS (STUDY 301)

Treatment	Race	n	Trough[a,b] (ng/mL)	C.V. (%) Interindividual	C.V. (%) Intraindividual
Rapamune 2 mg/day	Non-black	179	8.58 ± 3.98	46.4	37.8
	Black	47	8.62 ± 4.13	47.9	34.6
	Combined	226	8.59 ± 4.01	46.6	37.1
Rapamune 5 mg/day	Non-black	170	17.1 ± 7.45	43.5	38.6
	Black	49	17.7 ± 7.05	39.8	39.3
	Combined	219	17.3 ± 7.35	42.6	38.8

Source of Variation	P-value from ANOVA[c]
Treatment	0.050
Race	0.38
Treat * Race	0.39

a: Trough concentrations presented as mean ± SD.
b: Mean of average troughs (by area method) across days in individual patients.
c: Individual trough concentrations were normalized to 2 mg prior to ANOVA.

Results of univariate logistic regression analyses showed that higher Rapamune concentrations were significantly associated ($p < 0.001$) with decreased incidence of allograft rejection. No other significant trends among other explanatory variables were observed.

In summary, the efficacy results for black patients were not biased by differences in CsA trough levels between black and non-black patients in study 301. Additionally, there did not appear to be an intrinsic difference in the pharmacokinetics profiles of Rapamune in black patient versus non-black patients and that for any patient, the risk of acute rejection decreases as Rapamune levels increase.

7.10.7.3 Analyses of the Composite Endpoint of Efficacy Failure, Biopsy-Confirmed Acute Rejection, and Treatment Failure by Race

Studies 301 and 302 tested the effect of 2 dose levels of Rapamune on a composite endpoint of efficacy failure (acute rejection, graft loss or death) at 6 months following transplantation. The analysis of efficacy failure with respect to black patients by treatment group failed to show a significant decrease in efficacy failure rates in the Rapamune groups compared to the control groups (section 7.7.1). These results may be partially explained by the small numbers of black patients in the

control groups. Therefore an analysis that compared the efficacy endpoints between black and non-black patients was performed

There were significantly higher rates of efficacy failure and biopsy-confirmed acute rejection observed in black patients receiving Rapamune 2 mg/day than in non-black patients (Tables 7.10.7.3A and B). However, among patients in the Rapamune 5 mg/day group, there were no significant differences between efficacy failure rates in black patients compared to non-black patients. Additionally, the rates of biopsy-confirmed acute rejection and treatment failure in black patients in the Rapamune 5 mg/day treatment group were similar to those of non-black patients in the Rapamune 2 mg/day group (Tables 7.10.7.3B and C). Thus, there were positive treatment effects observed for black patients who received Rapamune 5 mg/day with regard to efficacy failure, biopsy-confirmed acute rejection and treatment failure.

These results suggest that Rapamune 5 mg/day in black patients confers a similar benefit to that of the Rapamune 2 mg/day dose in non-black patients and that the Rapamune 5 mg/day dose should be recommended for black patients. The benefit is most likely related to higher trough concentrations of Rapamune leading to decreased risk of rejection. These results also suggest that, since Rapamune overcomes the immunological resistance in these high risk patients, the drug may have benefit in other groups at high immunologic risk for acute rejection.

TABLE 7.10.7.3A. NUMBER (%) OF PATIENTS WITH EFFICACY FAILURE BY RACE (STUDY 301)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 5 mg/day 301 (n = 274)	Azathioprine 301 (n =161)
Black patients, n (%)	22/63(34.9)	11/61 (18.0)	14/42 (33.3)
Non-black patients, n (%)	31/221(14.0)	35/213(16.4)	38/119(31.9)
Fisher's exact p-value[a]	< 0.001	0.846	0.850

a: Fisher's exact p-values compare each dose of Rapamune in black patients to non-black patients.

TABLE 7.10.7.3B. NUMBER (%) OF PATIENTS WITH BIOPSY-CONFIRMED ACUTE REJECTION BY RACE (STUDY 301)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 5 mg/day 301 (n = 274)	Azathioprine 301 (n = 161)
Black patients, n (%)	19/63 (30.2)	9/61 (14.8)	12/42 (28.6)
Non-black patients, n (%)	29/221 (13.1)	4/213 (11.3)	36/119 (30.3)
Fisher's exact p-value[a]	0.004	0.504	1.000

a: Fisher's exact p-values compare each dose of Rapamune in black patients to non-black patients.

TABLE 7.10.7.3C. NUMBER (%) OF PATIENTS WITH TREATMENT FAILURE BY RACE (STUDIES 301)

Variable	Rapamune 2 mg/day 301 (n = 284)	Rapamune 5 mg/day 301 (n = 274)	Azathioprine 301 (n = 161)
Black Patients, n (%)	31/63 (49.2)	23/61 (37.7)	20/42 (47.6)
Non-Black Patients, n (%)	72/221 (32.6)	83/213 (39.0)	59/119 (49.6)
Fisher's Exact p-value[a]	0.018	0.626	0.859

a: Fisher's exact p-values compare each dose of Rapamune in black patients to non-black patients.

7.10.8 Determination of Drug Exposure

In order to evaluate effectiveness of Rapamune, it should be determined whether patients had an adequate drug exposure (duration, dose, discontinuations).

7.10.8.1 Duration of Exposure

Table 7.10.8.1A shows the numbers of patients pooled from studies 301 and 302, who were exposed to Rapamune by duration of exposure and mean daily dose. Patients receiving Rapamune therapy initially received a loading dose equal to 3 times the protocol-specified maintenance dose. The loading doses are included in the table. Sixty-nine (69%) percent of the patients randomized to receive Rapamune did so for at least 150 days (the 6 month data window was 154 to 194 days). Similarly, the numbers of patients who were receiving Rapamune at 28 and 90 days were 825 (84.5%) and 740 (75.8%), respectively. The majority of patients had mean doses of Rapamune of either 1.5 to 2.5 mg/day (n = 429) or 4.5 to 5.5 mg/day (n = 315) that encompassed the dose range of Rapamune intended for study (2 mg/day and 5 mg/day). The majority of the remaining patients received mean daily doses between 2.5 to 4.5 mg/day, again within the dose range for the two studies. These results suggest that patients enrolled in the Rapamune treatment groups were adequately exposed to potentially therapeutic doses of drug.

TABLE 7.10.8.1A. NUMBER OF PATIENTS EXPOSED TO RAPAMUNE BY DURATION OF EXPOSURE AND MEAN DAILY DOSE

Duration of Total Exposure to a Given Dose (days)	Rapamune Total Daily Dose (mg)					
	< 1.5	1.5 to 2.5	>2.5 to 4.5	4.5 to 5.5	> 5.5	Any Dose
1 day (1 dose)					9	9
2 to 14 days		22	36	4	42	104
15 to 28 days	2	15	5	10	6	38
29 to 60 days		20	6	26		52
61 to 90 days	1	15	2	15		33
91 to 120 days	1	15	9	13		38
121 to 150 days		15	4	13		32
151 to 180 days	19	148	40	96		303
181 to 210 days	15	179	35	138		367
Total	38	429	137	315	57	976[a]

a: A single patient in protocol 302 in the Rapamune 5 mg/day group was mistakenly identified as having received study drug; therefore, 976 is the correct number of patients who received at least 1 dose of Rapamune.

7.10.8.2 Dose Reduction

Evaluation of dose reduction in studies 301 and 302 is as follows:

- Of the 976 patients who received at least 1 dose of Rapamune, 627 (64.2%) patients did not have a dose reduction.
    - * Of the 627 patients who did not require a dose reduction, 431 (68.7%) patients received at least 154 days of dosing with Rapamune.
- Among 284 control patients (those who received at least one dose of placebo or azathioprine), 221 (77.8%) did not require temporary or permanent dose reduction.

These results demonstrate that the proportion of patients who required temporary or permanent dose reduction was higher in the Rapamune 5 mg/day group (42.8%) than the Rapamune 2 mg/day group (29.1%); dose-reduction in the Rapamune 2 mg/day group (29.1%) was similar to that observed in the combined control groups (22.2%) group. With the information provided in the previous section, it is shown that patients randomly assigned to the Rapamune treatment groups received adequate exposure to the drug for the purpose of demonstrating efficacy.

7.10.8.3 Discontinuations from Dose Administration (6 Months)

Table 7.10.8.3A shows the number of patients pooled from studies 301 and 302 who discontinued drug therapy (or never started drug therapy) by reason for each treatment group (see section 8.5 for discontinuations at 12 months by study). There were 35 patients who never received study drug (n = 12, Rapamune 2 mg/day; n = 16, Rapamune 5 mg/day; n = 1, azathioprine; and n = 6, placebo). The most common reasons for not receiving study drug were the occurrence of acute tubular necrosis (ATN) or increased creatinine (n = 10) or protocol violations (n = 19). The overall rate of discontinuation from the drug therapy was lower among the Rapamune treatment groups (33.4% in the Rapamune 2 mg/day group, 38.5% in the Rapamune 5 mg/day group) than in the placebo group (45.4%) and the azathioprine group (44.7%); pairwise comparisons of Rapamune 2 mg/day vs azathioprine and placebo were significant (p = 0.011 and p = 0.014, respectively). The most frequent reason for discontinuation in the Rapamune 2 mg/day and control groups was an unsatisfactory efficacy response; the most frequent reason in the Rapamune 5 mg/day group was adverse event.

TABLE 7.10.8.3A. NUMBER (%) OF PATIENTS WHO DISCONTINUED DURING THE DOSING PHASE (OR NEVER RECEIVED STUDY DRUG) BY TREATMENT GROUP (STUDIES 301 AND 302, 6-MONTH DATA)

	Treatment Group			
Reason for Discontinuation	Rapamune 2 mg/day (n = 511)	Rapamune 5 mg/day (n = 493)	Azathioprine (n = 161)	Placebo (n = 130)
Adverse event	33 (6.5)	57 (11.6)	15 (9.3)	8 (6.2)
Failed to return	1 (< 1)	1 (< 1)	1 (< 1)	0
Other medical event	39 (7.6)	42 (8.8)	10 (6.2)	13 (10.0)
Patient request	20 (3.9)	26 (5.3)	6 (3.7)	9 (6.9)
Protocol violation	12 (2.3)	16 (3.2)	4 (2.5)	1 (< 1)
Unsatisfactory response - efficacy	61 (12.0)	45 (9.1)	34 (21.1)	28 (21.5)
Other non-medical event	5 (1.0)	3 (< 1)	2 (1.2)	0
Total	171 (33.4)	190 (38.5)	72 (44.7)	59 (45.4)

Table 7.10.8.3B summarizes the number of patients (who did not have an acute, biopsy-confirmed rejection episode, graft loss or death, or who were lost to follow-up) who discontinued study drug before the 6 month efficacy time point, by treatment group. Patients assigned to receive Rapamune 5 mg/day had a numerically but not significantly (overall p = 0.142) higher rate of discontinuation from dosing (20.7%) than patients in the Rapamune 2 mg/day (14.9%), placebo (17.7%) or azathioprine groups (18.0%).

TABLE 7.10.8.3B. NUMBER (%) OF PATIENTS (WHO DID NOT HAVE AN EPISODE OF ACUTE BIOPSY-CONFIRMED REJECTION, GRAFT LOSS OR DEATH) DISCONTINUING FROM THE DOSING PHASE BY TREATMENT GROUP[a]

	Treatment Group			
Discontinuations	Rapamune 2 mg/day (n = 511)	Rapamune 5 mg/day (n = 493)	Azathioprine (n = 161)	Placebo (n = 130)
Up to 6 Months[b]	77 (14.9)	102 (20.7)	29 (18.0)	23 (17.7)

a: Excludes patients who had an episode of acute biopsy-confirmed rejection, graft loss, or death. Also excludes patients lost to follow-up at the 6 month efficacy time point.
b: Overall p value = 0.142, Fishers exact test.

7.10.9 Drug Level Relationship to Effectiveness

7.10.9.1 Results of Phase III Studies

Whole blood samples for pharmacokinetic profiling were analyzed for Rapamune by a validated method with an MQC (minimal quantifiable concentration) of 0.10 ng/mL. Whole blood Rapamune trough samples were analyzed using a validated with an MQC of 1.5 ng/mL. The influence of Rapamune and CsA concentrations on acute rejection was examined using step-wise logistic regression; data used were limited to months 1-2 (75 days).

7.10.9.1.1 Rapamune Exposure on Repeated Administration

Trough levels of Rapamune were extensively measured in both phase III studies. Overall, the findings for Rapamune trough levels between the two studies were similar and are summarized in Table 7.10.9.1.1A.

TABLE 7.10.9.1.1A. AVERAGE TROUGH WHOLE BLOOD RAPAMUNE CONCENTRATIONS IN RENAL ALLOGRAFT RECIPIENTS[a] (STUDIES 301 AND 302)

	Rapamune Treatment Group			
Variable	2 mg/day Study 301 (n = 226)	2 mg/day Study 302 (n = 212)	5 mg/day Study 301 (n = 219)	5 mg/day Study 302 (n = 206)
Trough (ng/mL)[b]	8.59 ± 4.01	8.06 ± 4.03	17.3 ± 7.35	17.3 ± 8.2
Inter individual CV[c] (%)	46.6	49.9	42.6	47.2

a: Trough concentrations presented as mean ± S.D.
b: Mean of average troughs (by area method) across days in individual patients.
c: CV = coefficient of variation.

Unlike study 302, pharmacokinetic profiles were obtained in study 301 at selected centers. The results showed that the average (range) trough whole blood Rapamune concentrations for the assigned Rapamune 2 mg/day and 5 mg/day dose groups were 8.59 (2.43 to 26.7) ng/mL and 17.3 (4.85 to 49.9) ng/mL, respectively. There were no significant differences in whole blood Rapamune steady-state pharmacokinetic parameters with respect to either Rapamune dose (2 mg/day or 5 mg/day), period (months 1, 3, and 6), or race (black, non-black). Although the whole blood Rapamune CL/F/W values among blacks and non-blacks were not significantly different, the mean CL/F/W values for blacks were decreased 22.8% in the Rapamune 2 mg/day group and 37.6% in the Rapamune 5 mg/day group compared to non-blacks. Dose proportionality was suggested based on a ratio of 2.51 for the mean $AUC_{\tau,ss}$ values of the Rapamune 2 mg/day (158 ng·h/mL) and Rapamune 5 mg/day (396 ng·h/mL) dose groups. The intersubject/intrasubject variabilities for the assigned Rapamune 2 mg/day and 5 mg/day dose groups were 46.6%/37.3% and 42.6%/38.8%, respectively.

7.10.9.1.2 CsA Trough Levels

Trough levels of CsA were extensively measured in both phase III studies. Overall, the findings for CsA trough levels between the two studies were similar and are summarized in Table 7.10.9.1.2A.

TABLE 7.10.9.1.2A. AVERAGE TROUGH WHOLE BLOOD CsA CONCENTRATIONS (ng/mL) OVER TIME IN RENAL ALLOGRAFT RECIPIENTS[a] (STUDIES 301[b] AND 302[c])

	Rapamune 2 mg/day		Rapamune 5 mg/day		Azathioprine	Placebo
	301	302	301	302	301	302
Trough (ng/mL)	(n = 284)	(n = 227)	(n = 274)	(n = 219)	(n = 161)	(n = 130)
Month 1	363 (40.7)[d]	412 (95.5)	363 (51.5)	372 (28.7)	378 (44.4)	374 (34.5)
Months 2-3	319 (43.8)	333 (31.3)	298 (34.8)	328 (30.4)	307 (24.0)	316 (27.5)
Months 4-6	268 (33.8)	262 (29.0)	250 (33.8)	266 (38.7)	260 (26.2)	284 (26.7)

a: Mean of average troughs (by area method) across days in individual patients.
b: ANOVA p-Value for study 301 (treatment) = 0.67.
c: ANOVA p-Value for study 302 (treatment) = 0.001.
d: Intersubject %CVs.

For study 301, there were no differences in trough whole blood CsA levels among treatment groups. The intersubject/intrasubject variabilities in CsA troughs for the assigned placebo, Rapamune 2 mg/day and 5 mg/day dose groups were 26.2%/18.6%, 33.8%/29.2%, and 33.8%/24.5%, respectively. For study 302, there were significant differences among the treatment groups in actual whole blood CsA concentrations thought to be related to elevated concentrations in black patients receiving 2 mg/day Rapamune during month 1.

7.10.9.1.3 Cyclosporine Dose Requirements

As shown in Tables 7.10.9.1.3A and B, the dose requirements for CsA were approximately 10-15% lower for Rapamune-treated patients as compared to the azathioprine and placebo controls.

TABLE 7.10.9.1.3A. MEAN CYCLOSPORINE DOSES (mg): STUDY 301, 6 MONTHS

Treatment	Month 1	Months 2 to 3	Months 4 to 6
Rapamune 2 mg/day	568	432	364
Rapamune 5 mg/day	528	410	343
Azathioprine	601	501	409

TABLE 7.10.9.1.3B. MEAN CYCLOSPORINE DOSES (mg): STUDY 302, 6 MONTHS

Treatment	Month 1	Months 2 to 3	Months 4 to 6
Rapamune 2 mg/day	532	378	305
Rapamune 5 mg/day	528	357	283
Placebo	544	416	348

7.10.10 Efficacy Conclusions

Primary Endpoint: Efficacy Failure

- Rapamune 2 mg/day and 5 mg/day significantly reduced the incidence of the composite endpoint of efficacy failure (first occurrence of biopsy-confirmed acute rejection, graft loss, or death) compared to control therapies during the first 6 months after transplantation. Patients in the Rapamune 2 mg/day group had approximately a 40% decrease in the rate of efficacy failure; those in the Rapamune 5 mg/day group had approximately a 50% decrease in the rate of efficacy failure. This positive treatment effect was observed in both studies.

- Analyses of efficacy failure in demographic subpopulations support treatment with Rapamune for the majority of primary renal transplant patients; all subgroups of patients demonstrated incidences of efficacy failure similar to or better than that of the control groups.

    * Significant improvement in the rates of efficacy failure for the following subgroups of patients: male patients, white patients, patients between 18 and 65 years of age, and patients with 4-6 HLA-mismatches.

- No significant positive or negative effects on efficacy failure rates for the remaining subgroups of patients. Black patients in study 301 had a numerically lower efficacy failure rate in the Rapamune 5 mg/day group (18%) than in either the Rapamune 2 mg/day group (34.9%) or the azathioprine group (33.3%), although the differences were not statistically different. Fewer black patients were enrolled in study 302; the rates of efficacy failure were greater than 30% in all treatment groups.

- Although a statistical advantage could not be demonstrated for black patients in either Rapamune dose group compared to either of the control therapies, pharmacokinetics and pharmacodynamic data as well as the results of the black versus non-black analysis for efficacy failure support the use of the Rapamune 5 mg/day dose in patients at high risk for acute rejection including, but not be limited to: African American patients (black patients), those receiving second or third transplants, those with high levels of pre-formed antibody (ie, high panel reactive antibodies), and those with high degrees of HLA mismatch).

***Acute Rejection*:**

- Rapamune 2 mg/day and 5 mg/day significantly reduced the incidence of the first biopsy-confirmed acute rejection episode compared to control therapies during the first 6 months after transplantation. Again, patients in the Rapamune 2 mg/day group had approximately a 40% decrease in the rate of biopsy-confirmed acute rejection and those in the Rapamune 5 mg/day arm had a 55-60% reduction in the incidence of biopsy-confirmed acute rejection. The effectiveness of Rapamune is underscored by the low rate of rejection in the azathioprine group.

- The use of anti-T lymphocyte antibody therapies to treat the first biopsy-confirmed acute rejection episodes during the first 6 months after transplantation was significantly lower in the Rapamune groups than in the control groups. This effect was demonstrated in both studies and was significant in all Rapamune groups with the exception of the Rapamune 2 mg/day group in study 302, where there was a numerical advantage that did not reach statistical significance.

- Both studies demonstrated that treatment of renal allograft recipients with Rapamune altered the distribution of histologic severity grade of rejection in favor of Rapamune.

***Other Endpoints*:**

- There was a significant reduction in the incidence of treatment failure, defined as the first occurrence of biopsy-confirmed acute rejection or premature discontinuation from study medication for any reason (Rapamune 2 mg/day, studies 301 and 302) during the first 6 months after transplantation.
- Overall 1-year patient and graft survival (≥ 95% and ≥ 89.9%, respectively) were excellent.
- The pharmacokinetic and pharmacodynamic data demonstrate that:
    * unlike CsA, Rapamune trough concentrations are linear with dose and are unaffected by race (black versus non-black).

The two phase III studies were similar but not identical in terms of study design and yielded the following efficacy results that were complementary.

- Comparator: Rapamune clearly demonstrated significantly improved rates of efficacy failure, of first acute rejection episodes, and of treatment failure over placebo and an active comparator, azathioprine.

- Stratification: When stratified by race (study 301) and donor source (study 302), the results of the analyses of the rates of efficacy failure support the results obtained in the primary efficacy analyses.
- Time of randomization: The effect of this variable was best demonstrated by comparing the rates of patients randomized but not dosed in the 2 studies (1.2 %, study 301 vs 4.5%, study 302). Both studies demonstrated the effectiveness of Rapamune in preventing efficacy failure, regardless of the time of randomization, thus eliminating a selection bias as the basis for the positive treatment effect shown in study 301.

In summary, two adequate and well-controlled phase III trials, similar but not identical in design, yielded comparable results of multiple primary and secondary efficacy analyses that support the use of Rapamune to prevent acute rejection in renal allograft recipients.

- Based on the results of the phase III studies, blood monitoring is not required to achieve a good clinical result in most patients treated with CsA and Rapamune

8 SAFETY

8.1 Overview

This section summarizes the safety data for the patients in studies 301 and 302 who were exposed to at least one dose of Rapamune, and presents key phase 3 safety data, which includes information through one year and in some instances beyond one year. Combined data are presented as integrated results of the two studies. For selected safety parameters, data are also presented by study to highlight similarities or differences.

8.2 Patient Populations

Table 8.2A shows the patient populations in studies 301 and 302.

8.2A. PATIENT POPULATIONS

Studies Included	Description	Randomized Treatments	Total Patients (n = 1260[a])
Protocol 301[b] Protocol 302[b]	Adequate and well-controlled trials in renal allograft recipients	Rapamune	Rapamune = 976
		Azathioprine (study 301)	Azathioprine = 160
		Placebo (study 302)	Placebo = 124

a: Of the 1295 enrolled, 1260 patients received randomized treatment.
b: All cumulative data, including patient death and graft losses.

8.3 Extent of Exposure

This section describes the patients who were exposed to at least one dose of Rapamune in studies 301 and 302. Patients receiving Rapamune therapy received an initial loading dose of 3 times the protocol-specified maintenance dose. Of the 1260 patients enrolled in studies 301 and 302, 976 patients received at least one dose of Rapamune.

Of the 976 patients who received at least one dose of Rapamune, 679 (69.6%) received Rapamune for at least 150 days (within the 6-month window), and 552 (57%) received it for more than 330 days (within the 12-month window). Of the 679 patients who received any dose of Rapamune for > 150 days, 630 had an average dose of at least 1.5 mg. Of the 552 patients who received any dose of Rapamune for more than 330 days, 515 had an average dose of at least 1.5 mg. The majority of patients had mean doses of Rapamune of either 1.5 to 2.5 mg/day (n = 426) or 4.5 to

5.5 mg/day (n = 292), which encompassed the dose range of Rapamune intended for study (2 mg/day and 5 mg/day). The majority of the remaining patients received mean daily doses between 2.5 and 4.5 mg/day, again within the dose range for this study.

8.4 Demographic Characteristics of the Study Population

The demographic characteristics of the efficacy population (all randomized patients) are displayed by study in Table 7.5A and closely mirror those of the safety population (patients who received at least one dose of study drug). The only demographic differences between the studies were that in study 301, a greater proportion of women than men were randomly assigned to the azathioprine group than to the Rapamune groups, and in study 302, a lower percentage of black and Hispanic patients were enrolled in all groups than in study 301.

8.5 Discontinuations

Tables 8.5A and 8.5B show the number of patients by treatment group in studies 301 and 302, respectively, who discontinued drug therapy and the reasons for discontinuation (see section 7.10.8.3 for 6 month combined data). In study 301, there was no difference among the treatment groups in the overall rate of discontinuation from study drug, whereas in study 302 a significant difference occurred (the rate was lowest in the Rapamune 2 mg/day group). In both studies, the most frequent reason for discontinuation in the Rapamune 2 mg/day, azathioprine, and placebo groups was unsatisfactory response to treatment. In both studies, a significant difference was seen among study groups for unsatisfactory response to treatment (rates were highest in the control groups). The most frequent reason for discontinuation in the Rapamune 5 mg/day groups was adverse reaction. In study 301, the rate of discontinuation from study drug because of adverse events was numerically but not significantly higher in the Rapamune 5 mg/day group, whereas in study 302 there was a significant difference among the groups (the rate was highest in the Rapamune 5 mg/day group).

TABLE 8.5A. NUMBER (%) OF PATIENTS WHO DISCONTINUED DURING THE TREATMENT PHASE BY TREATMENT GROUP (STUDY 301, 12 MONTHS)

Reason	Rapamune 2 mg/day (n = 284)	Rapamune 5 mg/day (n = 274)	Azathioprine (n = 161)	Fisher's Exact p-Value
Adverse reaction	27 (9.5)	43 (15.7)	18 (11.2)	0.0778
Failed to return	4 (1.4)	1 (< 1)	1 (< 1)	0.4541
Other medical event	21 (7.4)	28 (10.2)	10 (6.2)	0.2985
Other non-medical event	9 (3.2)	3 (1.1)	5 (3.1)	0.1884
Patient/subject request	17 (6.0)	12 (4.4)	9 (5.6)	0.6834
Protocol violation	15 (5.3)	15 (5.5)	4 (2.5)	0.3111
Unsatisfactory response - efficacy	42 (14.8)	29 (10.6)	35 (21.7)	0.0073
Total	135 (47.5)	131 (47.8)	82 (50.9)	0.7675

TABLE 8.5B. NUMBER (%) OF PATIENTS WHO DISCONTINUED DURING THE TREATMENT PHASE DATA BY TREATMENT GROUP (STUDY 302, 12 MONTHS)

Reason	Rapamune 2 mg/day (n = 227)	Rapamune 5 mg/day (n = 219)	Placebo (n = 130)	Fisher's Exact p-Value
Adverse reaction	23 (10.1)	40 (18.3)	9 (6.9)	0.0036
Failed to return	0	0	0	N/A
Other medical event	23 (10.1)	25 (11.4)	14 (10.8)	0.9116
Other non-medical event	4 (1.8)	3 (1.4)	0	0.4407
Patient/subject request	10 (4.4)	19 (8.7)	10 (7.7)	0.1671
Protocol violation	1 (< 1)	2 (< 1)	1 (< 1)	0.8391
Unsatisfactory response - efficacy	30 (13.2)	31 (14.2)	31 (23.8)	0.0258
Total	91 (40.1)	120 (54.8)	65 (50.0)	0.0067

8.6 Analysis of Adverse Events

Presentation of adverse events in this safety update will be limited to treatment-emergent adverse events (TEAEs). Because of the concern that added immunosuppression would increase the risk of infection, adverse events are discussed in two subsets: adverse events excluding infection and adverse events related to infection.

A TEAE is defined as an event that was not present at baseline or that was present at baseline but worsened during treatment. This section summarizes the cumulative TEAEs by treatment group for all patients treated with Rapamune, azathioprine, and placebo.

8.6.1 TEAE Excluding Infection and Malignancy (≥ 20% Frequency)

The cumulative data base includes all available information on all patients, with a minimum of one year follow-up after transplantation. The overall frequency of TEAEs in the cumulative data base was at least 99% for any treatment group. Table 8.6.1A summarizes the most common TEAEs occurring in at least 20% of the patient population for any one treatment group. Pooled data for the 2 mg/day Rapamune and the 5 mg/day Rapamune groups are compared with the azathioprine and the placebo comparator from each of the individual studies.

TABLE 8.6.1A. NUMBER (%)[a] OF PATIENTS REPORTING TREATMENT EMERGENT ADVERSE EVENTS EXCLUDING INFECTION AND MALIGNANCY OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY ONE TREATMENT GROUP (CUMULATIVE DATA, STUDIES 301 AND 302)

Body System Adverse Event	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Any adverse event (1 or more)	497 (100)	474 (99)	159 (99)	124 (100)
Body as a whole				
Abdominal pain	141 (28)	155 (32)	47 (29)	37 (30)
Asthenia	153 (31)	167 (35)	59 (37)	35 (28)
Back pain	95 (19)	114 (24)	37 (23)	25 (20)
Chest pain	84 (17)	100 (21)	25 (16)	23 (19)
Fever [b*]	127 (25) [d,e]	161 (34)	52 (33)	44 (35)
Headache	140 (28)	144 (30)	34 (21)	39 (31)
Pain	140 (28)	139 (29)	48 (30)	31 (25)
Cardiovascular system				
Hypertension [b**]	219 (44) [c]	205 (43) [c]	46 (29)[f]	59 (48)
Digestive system				
Constipation	156 (31)	169 (35)	59 (37)	39 (31)
Diarrhea [b**]	144 (29)[e]	184 (39) [c,d]	44 (28)	33 (27)
Dyspepsia [b*]	99 (20)[d]	114 (24) [d]	38 (24)	42 (34)
Nausea [b*]	142 (28)[c]	162 (34)	63 (39)	36 (29)
Vomiting [b*]	101 (20)[c]	117 (25)	50 (31)	26 (21)
Hemic and lymphatic system				
Anemia [b**]	127 (25)[e]	168 (35) [d]	46 (29)	26 (21)
Leukopenia [b***]	45 (9)[c,e]	67 (14)	32 (20)[f]	10 (8)
Thrombocytopenia [b***]	66 (13)[e]	115 (24)[c,d]	15 (9)	11 (9)
Metabolic and nutritional				
Creatinine increased	183 (37)	183 (38)	44 (28)	47 (38)
Edema [b*]	112 (22)[e]	81 (17)	37 (23)	18 (15)
Hypercholesteremia [b***]	202 (40)[d]	209 (44)[c,d]	53 (33)	28 (23)
Hyperkalemia [b***]	80 (16)[c,d]	61 (13)[c,d]	38 (24)	33 (27)
Hyperlipemia [b***]	204 (41)[c,d,e]	236 (49)[c,d]	45 (28)	28 (23)
Hypophosphatemia	88 (18)	103 (22)	32 (20)	23 (19)
Peripheral edema [b*]	287 (58)	293 (61)[d]	92 (58)	59 (48)
Musculoskeletal system				
Arthralgia [b*]	124 (25)	137 (29)[d]	34 (21)	22 (18)
Nervous system				
Tremor	134 (27)	128 (27)	44 (28)	23 (19)
Respiratory system				
Dyspnea	116 (23)	138 (29)	37 (23)	37 (30)
Pharyngitis[g]	82 (16)	88 (18)	27 (17)	27 (22)
Upper respiratory infection [b*,g]	114 (23)[c]	112 (23)[c]	20 (13)	29 (23)
Skin and appendages				
Acne [b*]	133 (27)[c,e]	99 (21)	27 (17)	23 (19)

TABLE 8.6.1A. NUMBER (%)[a] OF PATIENTS REPORTING TREATMENT EMERGENT ADVERSE EVENTS EXCLUDING INFECTION AND MALIGNANCY OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY ONE TREATMENT GROUP (CUMULATIVE DATA, STUDIES 301 AND 302)

Body System Adverse Event	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Study event assoc. w/ misc. factor				
Local reaction to procedure	247 (49)	265 (56)	73 (46)	58 (47)

a: The percent is based on the total number of patients in the treatment group.
b: Fisher's p-value for overall significance among treatment groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. A hyphen indicates no significant overall p-value.
c: Pairwise comparison significant for 2 mg/day or 5 mg/day Rapamune versus azathioprine.
d: Pairwise comparison significant for 2 mg/day or 5 mg/day Rapamune versus placebo.
e: Pairwise comparison significant for 2 mg/day Rapamune versus 5 mg/day Rapamune.
f: Pairwise comparison significant for azathioprine versus placebo.
g: Upper respiratory infection was a newly created COSTART category after the 6-month NDA ISS data base was closed. Some terms categorized as pharyngitis in the NDA ISS are now categorized as upper respiratory infections.
h: Not applicable.

8.6.1.1 Clinically Important TEAEs Excluding Infection and Malignancy

TEAEs were identified as clinically important based on the incidence rates (overall rates and rates between treatment groups), relevance to the renal transplantation population, and/or safety data from previous Rapamune trials. Table 8.6.1.1A lists the frequency of clinically important TEAEs by treatment group, excluding infection and malignancy, for events that occurred with a frequency of > 5% and < 20%.

TABLE 8.6.1.1A. NUMBER (%)[a] OF PATIENTS WITH CLINICALLY IMPORTANT TEAEs OCCURRING IN > 5% AND < 20% OF THE PATIENTS IN A TREATMENT GROUP, EXCLUDING INFECTION AND MALIGNANCY: CUMULATIVE DATA, STUDIES 301 AND 302

Body System Adverse Event	Rapamune 2 mg/day (n = 499)	Rapamune 5 mg/day (n = 477)	Azathioprine (n = 160)	Placebo (n = 124)
Body as a whole				
Chills [b**]	38 (8)[e]	60 (13)[c]	8 (5)	13 (10)
Face edema [b***]	30 (6)[e]	63 (13)[c]	9 (6)	7 (6)
Lymphocele [b***]	62 (12)[c,d,e]	83 (17)[c,d]	8 (5)	7 (6)
Cardiovascular system				
Hypotension [b**]	28 (6)[c,e]	48 (10)	24 (15)	10 (8)
Tachycardia [b***]	60 (12)[c,d]	70 (15)[c,d]	8 (5)	6 (5)
Digestive System				
Liver function tests abnormal	41 (8)	59 (12)	16 (10)	11 (9)
Endocrine System				
Diabetes mellitus	41 (8)	49 (10)	13 (8)	5 (4)
Hemic and lymphatic system				
Thrombotic thrombocytopenic purpura [b*]	10 (2)[e]	26 (5)	3 (2)	4 (3)
Metabolic and nutritional				
ALT increased	38 (8)	35 (7)	8 (5)	9 (7)
AST increased	22 (4)	28 (6)	7 (4)	7 (6)
Healing abnormal	48 (10)	58 (12)	11 (7)	9 (7)
Hyperglycemia	76 (15)	86 (18)	30 (19)	15 (12)
Hypokalemia [b**]	70 (14)[e]	92 (19)[c,d]	18 (11)	11 (9)
LDH increased [b**]	57 (11)[e]	78 (16)[c,d]	13 (8)	8 (6)
Nervous system				
Hypotonia	28 (6)	34 (7)	6 (4)	8 (6)
Insomnia [b*]	67 (13)[e]	87 (18)[d]	28 (18)[f]	10 (8)
Respiratory system				
Epistaxis [b***]	26 (5)[c,e]	43 (9)[c,d]	1 (< 1)	2 (2)
Skin and appendages				
Hirsutism [b*]	36 (7)	56 (12)	5 (3)	11 (9)
Rash [b***]	57 (11)[c]	75 (16)[c,d]	9 (6)	8 (6)
Skin ulcer [b*]	14 (3)[e]	32 (7)	7 (4)	4 (3)
Urogenital system				
Hematuria	72 (14)	90 (19)	27 (17)	15 (12)

a: The percent is based on the total number of patients in the treatment group.
b: Fisher's p-value for overall significance among treatment groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. A hyphen indicates no significant overall p-value.
c: Pairwise comparison significant for 2 mg/day or 5 mg/day Rapamune versus azathioprine.
d: Pairwise comparison significant for 2 mg/day or 5 mg/day Rapamune versus placebo.
e: Pairwise comparison significant for 2 mg/day Rapamune versus 5 mg/day Rapamune.
f: Pairwise comparison significant for azathioprine versus placebo.

8.6.2 Analysis of TEAEs, Excluding Infection and Malignancy, By Individual Study

The following TEAEs, which were both clinically relevant and statistically significantly different in either Rapamune group compared to the respective control group, are presented by study in Table 8.6.2A. The incidence of the events shown are ≥ 5% as defined by that incidence rate in any treatment group in either of the studies. This table includes events which were > 20% whereas in the previous integrated analyses these data were presented in separate tables.

Comparisons to the integrated data are as follows:

- Anemia, epistaxis, hyperkalemia, hyperlipemia, hypokalemia, lymphocele, rash, tachycardia, and thrombocytopenia are significantly different in one or both Rapamune groups compared with the control group for the individual studies and the integrated analysis.

- Acne, arthralgia, diarrhea, face edema, fever, hirsutism, hypercholesterolemia, hypertension, hypotension, LDH increased, leukopenia, and upper respiratory infection were significantly different in Rapamune-treated patients versus control patients in only one of the two studies. These events are also significantly different in Rapamune-treated patients versus one or both control groups in the previously displayed integrated data analyses.

- Asthma, dysuria, and ecchymosis are significantly different in Rapamune-treated patients compared with controls in individual studies but not in the integrated analysis.

- Dyspepsia, nausea, vomiting, and peripheral edema are significantly different in the Rapamune-treated patients compared with control group in the integrated analysis only.

TABLE 8.6.2A. NUMBER (%)[a] OF PATIENTS WITH TEAEs OCCURRING IN > 5% OF THE PATIENTS IN A TREATMENT GROUP, EXCLUDING INFECTION AND MALIGNANCY: INDIVIDUAL STUDIES 301 AND 302

Body System Adverse Event	Rapamune 2 mg/day (n = 281)[b] (n = 218)[c]	Rapamune 5 mg/day (n = 269)[b] (n = 208)[c]	Azathioprine (n = 160)[b]	Placebo (n = 124)[c]
Acne				
Study 301	86 (31)[f,d]	54 (20)	27 (17)	
Study 302	47 (22)	45 (22)		23 (19)
Anemia				
Study 301	76 (27)[f]	100 (37)	46 (29)	
Study 302	51 (23)[f]	68 (33)[e]		26 (21)
Arthralgia				
Study 301	69 (25)	73 (27)	34 (21)	
Study 302	55 (25)	64 (31)[e]		22 (18)
Asthma				
Study 301	17 (6)[d]	16 (6)[d]	2 (1)	
Study 302	10 (5)	9 (4)		4 (3)
Back Pain				
Study 301	45 (16)[f]	69 (26)	37 (23)	
Study 302	50 (23)	45 (22)		25 (20)